IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC. and JANSSEN PHARMACEUTICA NV, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 2:18-00734 (CCC)(MF) [redacted] *Electronically Filed*

DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S
POST-TRIAL BRIEF

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	D.I. 91	Janssen Pharmaceuticals Inc. and Janssen Pharmaceutica, NV's Motion for Correction of Inventorship Pursuant to 35 U.S.C. § 256
	DTX-2/ PTX-2	File History of U.S. Patent No. 9,439,906
PTO	D.I. 133	Final Pretrial Order
'544 Patent	DTX-54/ PTX-55	U.S. Patent No. 6,555,544 to François et al.
'548 Regimen	DTX-55/ PTX-54	NCT00210548 Summary on ClinicalTrials.gov
'556 Patent	DTX-69	U.S. Patent No. 5,254,556 to Janssen et al.
'591 Application	DTX-108/ PTX-69	U.S. Patent Appl. Pub. No. 2007/0197591 to Boom et al.
'843 Patent	DTX-71	U.S. Patent No. 6,077,843 to François et al.
'906 Patent	DTX-1/ PTX-1	U.S. Patent No. 9,439,906 to Vermeulen et al.
'918 Provisional	PTX-76	U.S. Provisional Patent Application No. 61/014,918
'952 Patent	DTX-803	U.S. Patent No. 5,158,952 to Janssen et al.
150/25		An injection of 150 mg-eq. paliperidone on Day 1, and 25 mg-eq. on Day 8
150/100		An injection of 150 mg-eq. paliperidone on Day 1, and 100 mg-eq. on Day 8
150/150		Injections of 150 mg-eq. paliperidone on each of Days 1 and 8
150/100/100/100		An injection of 150 mg-eq. paliperidone on Day 1, and 100 mg-eq. on Days 8, 36, and 64
150/150/100/100		Injections of 150 mg-eq. paliperidone on each of Days 1 and 8, and 100 mg-eq. on Days 36 and 64
100/100		Injections of 100 mg-eq. paliperidone on

Abbreviation	Exhibit/ Docket Ref.	Full Description
		each of Days 1 and 8
100/100/100/100		Injections of 100 mg-eq. paliperidone on Days 1, 8, 36, and 64
75/75/50/50		Injections of 75 mg-eq. paliperidone on each of Days 1 and 8, and 50 mg-eq. paliperidone on Days 36 and 64
2007 Haldol Label	DTX-149/ PTX-592	HALDOL® Decanoate (Haloperidol) Intramuscular Injection Label, Revised 2007
ANDA		Abbreviated New Drug Application
Asserted Claims		Claims 2, 10, and 13, and claims 20 and 21 of U.S. Patent No. 9,439,906
BMI		Body Mass Index
C.C.P.A.		United States Court of Customs and Patent Appeals
CL		Defendant Teva Pharmaceuticals USA, Inc.'s Proposed Conclusions of Law
Cleton 2007	DTX-84/ PTX-56	"PII-46 Effects of Renal Impairment on the Pharmacokinetic Profile of Paliperidone Extended-Release Tablets," from Volume 81, Supplement 1 of Clinical Pharmacology & Therapeutics in March 2007.
Cleton 2008	DTX 18/ PTX-53; DTX-19; DTX-20	Collection of: 1. Abstracts PI-74 and PI-75 from Volume 83, Supplement 1 of Clinical Pharmacology & Therapeutics, March 2008. 2. Two posters associated with PI-74 and PI-75, respectively, presented at the American Society for Clinical Pharmacology & Therapeutics ("ASCPT") in Orlando, Florida from April 2–5, 2008
CQA		Critical Quality Attributes

Abbreviation	Exhibit/ Docket Ref.	Full Description
Dep.		Deposition
Einarson	PTX-134	T.R. Einarson, et al., *Economic and Clinical Comparison of Atypical Depot Antipsychotic Drugs for Treatment of Chronic Schizophrenia in the Czech Republic*, J. Med. Econ., 16(9):1089-93 (2013)
Emsley	PTX-133	R. Emsley, et al., *Efficacy and Safety Profile of Paliperidone Palmitate Injections in the Management of Patients with Schizophrenia: An Evidence-Based Review*, Neuropsychiatric Disease & Treatment (14):205-223 (2018) "
EP'081	DTX-799	European Patent No. 0,904,081
EP'987	DTX-800	European Patent No. 1,033,987
Ereshefsky 1990	DTX-88/ PTX-59	L. Ereshefsky et al., *Kinetics and Clinical Evaluation of Haloperidol Decanoate Loading Dose Regimen*, Psychopharmacol. Bull. 26(1):108-114 (1990)
Ereshefsky 1993	DTX-89/ PTX-60	L. Ereshefsky et al., *A Loading-Dose Strategy for Converting from Oral to Depot Haloperidol*, Hosp. & Cmty. Psychiat. 44(12):1155-1161 (1993)
FDA		U.S. Food and Drug Administration
FF		Defendant Teva Pharmaceuticals USA, Inc.'s Proposed Findings of Fact
FRE		Federal Rule of Evidence
Gibaldi	DTX-91	S. Bhalla, *Parenteral Drug Delivery*, in Gibaldi's Drug Delivery Systems in Pharmaceutical Care (A. Desai & M. Lee, eds. 2007)
Goodman	DTX-93	Goodman & Gilman's the Pharmacological Basis of Therapeutics (L. L. Brunton et al., 11th ed. 2006) and/or (10th ed. 2001).
IM		Intramuscular injection

Abbreviation	Exhibit/ Docket Ref.	Full Description
Invega ER Label	DTX-102/ PTX-57	Invega™ (paliperidone) Extended-Release Tablets Label for NDA 21999, Revised 2006
Invega IR		Janssen's immediate release paliperidone injectable drug product
IS		Invega Sustenna
IS Label		Invega Sustenna© Label
Janicak	DTX-58/ PTX-67	P.G. Janicak & E. A. Winans, *Paliperidone ER: A Review of the Clinical Trial Data*, Neuropsychiat. Disease & Treatment 3(6):869-883 (2007)
Janssen		Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV
Janssen's Rule 52(c) Motion	D.I. 139	Plaintiffs' Motion for Judgment on Partial Findings Under Rule 52(c) Dismissing Defendant's Counterclaims and Defenses on patent Invalidity
Karagianis	DTX-96/ PTX-63	J. L. Karagianis et al., *Rapid Tranquilization with Olanzapine in Acute Psychosis: A Case Series*, J. Clin. Psychiat. 62(suppl. 2):12-16 (2001)
"Lawrence" or "Lawrence & Taylor supplements"	PTX-506	Lawrence et al., *Paliperidone palmitate: a new long-acting injection for schizophrenia*, Therapeutic Advances
NIH		National Institutes of Health
OB		Approved Drug Products with Therapeutic Equivalence Evaluations
Orange Book		Approved Drug Products with Therapeutic Equivalence Evaluations
PANSS		Positive and Negative Syndrome Scale
PK		Pharmacokinetic
POSA		Person of Ordinary Skill in the Art
QALYs		quality-adjusted life years

Abbreviation	Exhibit/ Docket Ref.	Full Description
Representative Claims		Claims 2, 10, and 13, and claims 20 and 21 of U.S. Patent No. 9,439,906
SF	D.I. 133 at 4-16	The parties' Stipulation of Facts set forth in the Final Pretrial Order
Teva		Teva Pharmaceuticals USA, Inc.
Teva's 2009 patent application	PTX-813	U.S. Patent Appl. Pub. No. 2009/0209757 to Ini et al.
Teva's ANDA		Teva's Abbreviated New Drug Application No. 211149
Tr.		Transcript
USP		United States Pharmacopeia
"USPTO " or "PTO"		United States Patent and Trademark Office
Verm.		Vermeulen
Walsh Decl.		December 11, 2020 Declaration of Liza M. Walsh In Further Support of Defendant Teva Pharmaceuticals USA, Inc.'s Trial Brief and Findings of Fact and Conclusions of Law
Werm.		Wermeling
WO'384	DTX-72/ PTX-66	International Patent Application Publication No. WO 2006/114384

I. INTRODUCTION

The fundamental issue before the Court is whether the claims of the '906 Patent meet the statutory conditions and requirements of the Patent Act: 35 U.S.C. §§ 103 and 112. Clear and convincing evidence set forth at trial establishes that the law is not satisfied. The Court, therefore, should hold the claims invalid.

The Supreme Court in 2007 reemphasized that the proper § 103 analysis "is objective" and that when a court "conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). The reason for this is simple: a patent claiming obvious subject matter "withdraws what already is known into the field of its monopoly and diminishes the resources available to skillful men." *Id*. at 415–16. Here, the '906 Patent claims a monopoly over dosing regimens for administering paliperidone palmitate that were already known to people of skill in the art.

Each Representative Claim[1] is directed to monthly dosing regimens for administering a well-known drug, paliperidone palmitate, as part of known sustained-release formulations, for their known purpose to treat schizophrenia. The claimed regimens recite injecting into the deltoid muscle two loading doses of a

[1] Janssen has held out claims 2, 10, 13, 20, and 21 as being representative of all claims of the '906 Patent. (D.I. 133 at 9). Thus, if the Representative Claims are obvious, the '906 Patent as a whole is obvious.

particular amount over a range of alternative days, followed by monthly maintenance injections. To be sure, Janssen expended time and resources conducting clinical trials and making predictive models to help it choose the dosing regimens it desired for the Invega Sustenna ("IS") label and to secure FDA approval to market its product accordingly. But selecting regimens that met Janssen's internal company objectives, or even determining optimal regimens, from a small set of effective options already known and patented, is the result of "ordinary innovation" and "not the subject of exclusive rights under the patent law." *KSR*, 550 U.S. at 427. Indeed, such "selection inventions" are presumed obvious under the law, and none of Janssen's alleged real-world evidence rebuts this presumption.

As of the priority date of the '906 Patent, a POSA knew how, where, when and how much of the formulation that became IS to administer to effectively treat schizophrenia. In fact, Janssen had already received several patents for its work on treating schizophrenia with this and other sustained-release paliperidone palmitate formulations. And the only alleged advantage of Janssen's chosen regimens, in comparison with other known regimens, is based on unproven modeling predicting the percentage of patients expected to have certain drug blood levels by certain times. Janssen has not alleged (and the evidence does not support) any new or different therapeutic result for treating schizophrenia due to the claimed regimens. In sum, nothing about the regimens that Janssen selected is novel or critical. Yet,

Janssen seeks to reclaim and monopolize obvious selections from known possibilities that had already been dedicated to the public. *KSR*, 550 U.S. at 415–16.

Teva has also shown that most Representative Claims are indefinite and lack adequate written description. If the claims "fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention," they are invalid as indefinite. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). And if the four corners of the specification do not "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date," the patent lacks written description. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The '906 Patent fails both tests.

Certain claims directed generally to dosing regimens for renally-impaired patients claim broader than what the inventor's actually possessed; the inventors did not invent a dosing regimen for patients with anything other than mild renal impairment, or using doses in excess of 100 mg-eq. Moreover, certain claims recite "average particle size (d50)" limitations. But the '906 Patent does not inform a POSA which measure of particle size to use to determine the bounds of those claims. Indeed, in that respect, the case is nearly indistinguishable from the Federal Circuit's decision in *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). Likewise, although certain claims require a "nanoparticle" formulation, this term lacks a defined meaning in the art, and the '906 Patent does not set the bounds

as to the size of particles that fall within the claims.

Accordingly, and as explained in detail below, Teva respectfully submits that each Representative Claim of the '906 Patent is invalid.

II. THE REPRESENTATIVE CLAIMS ARE *PRIMA FACIE* OBVIOUS

"Section 103(a) forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *KSR*, 550 U.S. at 406. The '906 Patent does not meet the conditions of § 103 for at least two reasons. *First*, the claims can be fairly categorized as a "selection invention": as Teva demonstrated at trial, they merely recite limitations selected from known options for known result-effective variables without requiring any particular outcome. Such inventions are presumed obvious under the law, and are unpatentable, unless the patentee is able to rebut that presumption. Janssen failed to do so here. *Second*, even without the legal presumption, Teva has shown that based on the prior art before the earliest alleged invention date, a POSA would have been motivated to practice the claimed regimens with a reasonable expectation of success.

The evidence is clear that prior to the alleged invention of the '906 Patent, a POSA was informed and enabled to effectively treat schizophrenia by administering loading and monthly deltoid injections of aqueous formulations of paliperidone

palmitate having particle sizes of about 900–1600 nm, in therapeutic doses of between 25 and 150 mg-eq. (FF 156, 161–63, 173, 183, 206, 217–18, 317–68). This knowledge defines the "threshold from which innovation" of the '906 Patent must be measured. *KSR*, 550 U.S. at 427. Moreover, "design incentives and other market forces would prompt variations of" that work, and "[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Janssen's alleged "discovery of [ ] optimum value[s] of [ ] result effective variable[s] in a known process," therefore, is within the skill of the art and not patentable. *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980).

The evidence overwhelmingly shows that when the proper test is applied objectively, the Representative Claims are obvious.

A. The Claims Recite Parameters Selected From Know Options and Therefore Are Presumed Obvious.

Each Representative Claim covers various alternative dosing regimens. One obvious regimen within the scope of the claims comprises administering 75–150 mg-eq. paliperidone palmitate (***amounts***) as a sustained release formulation, with injections on Day 1, 8, 36, and 64 (***times***) into the deltoid muscle (***site***). (FF 351, 376). Certain of the claims also recite a particular formulation and average particle size taught by the prior art. Importantly, the claims do not require any particular

result from practicing the recited dosing regimens with the recited formulations.

1. The Recited Particle Size Range Is Completely Encompassed By The Prior Art

There is no dispute that the specific formulation that became IS and which Janssen asserts is covered by the Representative Claims, was disclosed in the prior art WO'384 publication. (FF 193, 207–08). That formulation has the exact ingredients and concentrations as those in claims 19 and 20 of the '906 Patent, and therefore also has the same pH as recited in claim 21. (FF 194, 361). Indeed, the entire sample preparation disclosure of the '906 Patent is copied ***word-for-word*** from WO'384, (FF 208), underscoring that rather than teaching a new invention, the '906 Patent only removes knowledge and resources from the public domain. The only thing the '906 Patent does, then, is claim a d50 range encompassing specific d50 examples taught by the earlier prior art '544 Patent. (FF 161–163).

A POSA, however, already knew the average particle size of paliperidone palmitate significantly impacts the PK behavior of the formulation, (FF 152, 363), and according to the '544 Patent, should be "less than 2,000 nm." (FF 154). Because the WO'384 improves the composition and method of sterilizing an aqueous formulation over the '544 Patent, but its description of the paliperidone palmitate particle size in the formulation exactly parallels the '544 Patent teaching, it is not inventive to select a d50 of 1380 nm from the '544 Patent examples to use in the WO'384 formulation. (FF 162, 197–200, 202). Thus, the '544 Patent together with

WO'384 teach all the formulation limitations of the Representative Claims.

2. The Sites, Times, and Doses of Administration Claimed Are Identical To Or Overlapping With The Prior Art

In addition to knowing the claimed formulation and d50 range, before the earliest alleged invention date of the '906 Patent, a POSA knew how to treat schizophrenia with such a formulation. In fact, Janssen's '544 Patent taught that monthly intramuscular injections of aqueous, nanoparticle paliperidone palmitate formulations in a specified dose range are effective for treating schizophrenia, and ***claimed*** a method of treating schizophrenia by administering a "therapeutically effective amount of" paliperidone palmitate. (FF 115, 145, 172–176, 440–442).

Having been rewarded with a patent for this work and having listed that patent in the OB as covering IS with a use code U-543—"treatment of schizophrenia"—Janssen cannot now say that the '544 Patent did not teach a POSA how to treat schizophrenia by intramuscular injections of an aqueous paliperidone palmitate nanoparticle suspension. (FF 439). The law is clear: "prior art patents are presumed enabled" for all that they teach, including all "unclaimed (and claimed) material." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354–55 (Fed. Cir. 2003). There is no evidence of record to overcome this presumption for the '544 Patent or any other prior art Janssen patent. Rather, Janssen's expert, Dr. Sinko, expressly noted that he is "not offering an opinion that a person of skill in the art could not practice [claim 7 of the '544 Patent] without undue experimentation." (FF

320). Moreover, trial counsel stipulated on the record that IS is covered by claim 7 of the '544 Patent. (FF 442). The Court should find that a POSA knew how to treat schizophrenia with a therapeutically effective amount of an aqueous paliperidone palmitate nanoparticle suspension from the prior art '544 Patent and WO'384.

The time, site and amount of each injection claimed in the '906 Patent were also known as useful options in the prior art. In fact, the '906 Patent represents that "paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly" and that it was "formulated as an aqueous nano suspension as is described in [the '544 Patent]" (FF 115). The '544 Patent made clear that the paliperidone palmitate sustained-release formulations are to be administered intramuscularly at an interval of "about three weeks or more, in particular about 1 month," (FF 145), just like the interval between the 2nd and 3rd injections and between the 3rd and 4th injections of the Representative Claims: injections made in accordance with the claims on Days, 8, 36, and 64 would be 28 days apart.

Both sides' experts agree that a POSA would understand the "intramuscular" injections of the '544 Patent are to be administered in the deltoid or gluteal muscles. (FF 170, 188); *see Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379 (Fed. Cir. 2014) (finding a specific treatment regimen obvious in view of a broader prior art treatment regimen); *see*

also Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001) ("[T]he disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited.").

A POSA also knew that the '906 Patent formulation was to be administered in doses of 25-150 mg-eq. Specifically, WO'384 taught that the Table 6 formulation containing 156 mg/mL paliperidone palmitate was to be administered in volumes between 0.25 mL and 1.50 mL, depending on the dose needed. (FF 193, 205). There is no dispute this describes a dose range of 25-150 mg-eq. (FF 206).

Initiating treatment with injections of 50 mg-eq., 100 mg-eq., or 150 mg-eq. on Days 1 and 8, followed by subsequent injections monthly at the claimed dose amounts of 25-150 mg-eq., was also known to a POSA from the prior art. (FF 217). The '548 Regimen—a Janssen Phase III clinical protocol for treating schizophrenia with intramuscular injections of paliperidone palmitate—taught injecting 50, 100, or 150 mg-eq. of paliperidone palmitate on days 1, 8, 36 and 64. In other words, the '548 Regimen taught "loading doses on Days 1 and 8, followed by monthly dosing" thereafter. (FF 218).

3. A Presumption of Obviousness Applies

The Representative Claims simply recite selections from the limited prior art options, all of which were known to be useful for treating schizophrenia:

Claim 2 Regimen		
Known Times	**Known Sites**	**Known Amounts**
Day 1	Deltoid	150
Day 6-10	Deltoid	100
Day 27-48 (Monthly ±7)	Deltoid or Gluteal	25-150
Day 48-86 (Monthly ±7)	Deltoid or Gluteal	25-150

The law, therefore, presumes the Representative Claims obvious, because "the discovery of an optimum value of a variable in a known process is normally obvious." *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977) (citing *In re Aller*, 220 F.3d 454 (C.C.P.A. 1955)); *see also E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (same). Because the general conditions of the Representative Claims are disclosed in the prior art, it was not inventive to select points or ranges that met the company's subjective preferences. Even if Janssen had discovered the optimal regimen (it did not), that would also not warrant a patent. To the contrary, "[i]n cases involving overlapping ranges, . . . even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Where, as here "the claimed ranges are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap," for "[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *Id.* at 1329–30; *see also In re*

Applied Materials, Inc., 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("Such overlap itself provides sufficient motivation to optimize the ranges."). Accordingly, "where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Tyco Healthcare Grp. LP v. Mut. Pharm. Co., Inc.*, 642 F.3d 1370, 1372–73 (Fed. Cir. 2011) (citation and quotation marks omitted); *see also Synvina*, 904 F.3d at 1006; *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737–38 (Fed. Cir. 2013).

In *Synvina*, the Federal Circuit examined whether the choice of conditions for a chemical reaction (i.e., temperature, pressure, catalyst, and solvent) was patentable where the prior art performed the reaction "under somewhat different conditions." 904 F.3d at 1001. The court applied an obviousness presumption because "the prior art as a whole . . . taught the claimed reaction, as well as conditions either identical to or overlapping with those [claimed]." *Id.* at 1011. And although four independent variables—temperature, pressure, solvent, and catalyst—had to be simultaneously optimized to arrive at the claimed reaction, the court held the claim invalid because "the normal desire of scientists or artisans to improve upon what is already generally known" would "provide[] the motivation to determine where in a disclosed set of ranges is the optimum combination." *Id.* at 1011.

Likewise in *Galderma*, the Federal Circuit invalidated claims directed to methods of treating acne using 0.3 % adapalene and one or more inactive excipients.

737 F.3d at 734. The court noted that a prior art reference disclosed adapalene compositions for treating acne containing 0.01%–1% adapalene, including several exemplary formulations. *Id*. at 734–35. Other prior art taught either the specific inactive ingredients claimed, or inactive ingredients equivalent to those claimed. *Id*. at 735–36. The court noted that "[i]n these circumstances, where there is a range disclosed in the prior art, and the claimed invention falls within that range," a presumption of obviousness applies and "the burden of production falls upon the patentee to come forward with evidence" rebutting the presumption. *Id.* at 738.

Here, the prior art taught treating schizophrenia with the claimed formulation by administering doses identical to or overlapping with those claimed, at the exact time points claimed, into one of two muscles. (FF 309–12, 193, 202). And with respect to the formulation, Janssen did no more than select a d50 range for a formulation that was exactly disclosed in the art, where a d50 within the claimed range was also taught. (FF 153, 161–163, 193, 202, 309–310, 363–368). Here, no less than in *Synvina* and *Galderma*, "the normal desire of scientists to improve what is generally known" would motivate a POSA to optimize these three variables to determine "the optimum combination." *In re Peterson*, 315 F.3d at 1330. Accordingly, a presumption of obviousness applies to the Representative Claims.

B. Janssen Has Failed To Rebut The Obviousness Presumption

A patentee may overcome the presumption of obviousness by showing that

the invention "produce[s] a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *Aller*, 220 F.2d at 456. "A claimed range that demonstrates such unexpected results is referred to as a 'critical' range, and the patentee has the burden of proving criticality." *Synvina*, 904 F.3d at 1006; *see also Warner Chilcott Co. v. Teva Pharm. USA, Inc.*, 89 F. Supp. 3d 641, 655–56 (D.N.J. 2015) *aff'd*, 642 F. App'x 996 (Fed. Cir. 2016) ("Where the difference between the claimed invention and the prior art is some range or other variable within the claims, the patentee must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results.").

Importantly, "[u]nexpected results that are probative of nonobviousness are those that are different ***in kind and not merely in degree*** from the results of the prior art." *Galderma*, 737 F.3d at 739 (emphasis added). "Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time." *Id.*; *In re Budde*, 319 F.2d 242, 246 (1963) (no unexpected results where ranges of reaction time and temperature constituted a difference in degree rather than in kind); *Aller*, 220 F.2d at 456–57 (improved yields, measured by percentages, reflect a difference in degree, not in kind, and do not evidence unexpected results).

Here, Janssen has failed to show criticality by any metric. Janssen has provided no evidence that the range of claimed d50 values are somehow unexpected,

critical, or otherwise patentably distinct to overcome this presumption. *See, e.g.*, *Ex parte Qinyun Peng and Philip Linz,* Appeal 2017-009317, 2018 WL 6338537, at *4 (P.T.A.B. Nov. 15, 2018) (finding patentee failed to overcome a presumption of obviousness of a claimed d50 based on an absence of criticality).

The '906 Patent dosing regimen elements fare no better. Janssen does not and cannot dispute that the prior art '548 Regimens are, in fact, safe and effective for such treatment. (FF 216, 343, 348). In fact, Janssen sought FDA approval for the 100/100 mg-eq. regimen, administered on Day 1 and on Day 8, representing to the FDA its understanding that this regimen was safe and effective. (FF 92). Consistently, the FDA-approved label for IS describes four different large-scale studies analyzing various dosing regimens that differ from the ones claimed, all of which demonstrated efficacious treatment of schizophrenia. (FF 555, 565, 575).

Janssen believed the claimed regimen—the 150/100 regimen—was the "optimal" regimen, because it could get a higher percentage of patients to purportedly therapeutic paliperidone palmitate blood levels within the first week of treatment. (*See* FF 95–96, 577, 675). But there is no dispute that the 100/100 regimen was accepted by the FDA and was considered "a very good recommendation." (FF 92–93). The only issue for this regimen, in Janssen's view, was that it would not be "optimal" for all patients. But, of course, neither is the 150/100 regimen. (FF 96).

Moreover, Janssen's assertion that the claimed dosing regimen is "optimal" is

not proven experimentally, nor based on any measure of actual efficacy, but only on hypothetical predictions of the percentage of subjects who should experience a certain range of drug blood levels. (FF 95–96). This explanation is not compelling. First, whether these blood levels translate to efficacy or side effects in any patient was not (and could not be) part of their prediction. (FF 63). Second, the model is based on PK data from a variety of different formulations having different particle sizes, and thus does not correlate with the claimed d50 range. (FF 576). Moreover, in an attempt to validate the model, Dr. Samtani excluded data from patients who had received oral paliperidone to test for tolerance because it did not fit his predictions, something Dr. Gopal said one should not do. (FF 112). But even if his explanation for excluding this data were scientifically appropriate, his model still differs from the claimed regimens, which cover treating such patients. (FF 86). In any event, if these hypothetical predictions show anything, it is that with many other dosing regimens, the majority of patients reach the hypothetical target by Day 8 of treatment. The only difference is in the percentage of patients who were predicted to get there—a difference in degree, not kind:

Table 1: Percentage of Subjects Above 7.5 ng/mL on Trough Days 8 and 36, for Various Initiation Regimens'

Regimen	Day 8	Day 36
75/75 mg eq. Day 1/8 deltoid	64 %	68 %
100/100 mg eq. Day 1/8 deltoid	73 %	76 %
150/100 mg eq. Day 1/8 deltoid	84 %	84 %

(FF 96). The same is true for the site of administration. Indeed, Janssen's argument that "[i]f you don't give those two high-loading dose injections in the deltoid, it just doesn't work," (Tr. 39:1–6), is demonstrably false. To the contrary, administering the first dose in the gluteus versus deltoid produces a minimal difference in the percentage of patients that reach the hypothetical target at 1 week: 66% vs. 84%, (FF 587), a difference that can be attributed to too short of a needle used in the gluteal, which is unrelated to the claim limitations.[2] (FF 599–601, 605–606). But even if the predicted differences were meaningful, they are a difference in degree, not kind. *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (32–43% increase in stress-rupture "does not represent 'difference in kind'" required for unexpected results).

In fact, most uses of IS do not follow the claimed regimen. REDACTED

REDACTED

REDACTED

(FF 410, 448).

[2] Dr. Samtani never did any modeling of results from using a 2" needle for gluteal injections. (*See* FF 604).

Janssen's BEL-4 study confirms that the Day 8 injection, far from being critical, is not even needed. The results showed that the mean plasma levels of numerous subjects who received 50, 100, and 150 mg-eq. monthly doses of paliperidone palmitate, without loading doses, reached the model's hypothetical blood level threshold by Day 8, and often in as little as 24-72 hours. (FF 544-546).

But the Court need not rely on hypothetical predictions and Janssen's assumptions about therapeutic blood levels to guess at efficacy: clinical data confirm that Janssen's claimed regimens are not critical. In October 2007—months before the earliest alleged invention date of the '906 Patent— the results of the SCH-201 study were presented at the 20th U.S. Psychiatric and Mental Health Congress in Orlando, Florida. (FF 103). The study administered either 50 or 100 mg-eq. paliperidone palmitate in the gluteal muscle, without oral supplementation, on each of days 1, 8, and 36. (FF 105). The study concluded that for the treatment groups, PANSS total score improvement—an actual measure of clinical efficacy—was "significantly different from placebo from Day 8" and that the study showed "[r]apid onset (by Day 8) of symptom improvement versus placebo achieved for both the 50 and 100 mg-eq. doses of paliperidone palmitate, and this effect was maintained throughout the study." (*Id.*). Dr. Vermeulen further testified that Day 8 was the first time PANSS score was assessed in this study (FF 488); it is therefore possible, consistent with the observations of the BEL-4 study, that the treatment groups

showed significant difference in PANSS score from placebo and symptom improvement onset even more rapid than Day 8—the study was just not designed to measure it. (*Id.*).

Moreover, Janssen has not and cannot show that the dosing regimens claims for renally impaired subjects (claims 10 and 13) are critical—they are not even the regimens recommended for renally impaired patients in the IS label. (*Compare* FF 87, *with* SF 9). Nor were they tested in any controlled clinical trial. (FF 98).

In sum, the data establish that the claimed dosing regimens were some of many regimens known in the art that worked for the treatment of schizophrenia. Where, as here, "an unexpected increase in efficacy is measured by a small percentage . . . the result constitutes a difference in degree, not kind," and is insufficient to overcome the obviousness presumption. *Galderma*, 737 F.3d at 739.

C. Even Absent An Obviousness Presumption, The Evidence Establishes That The Clams Are Obvious.

Even absent a presumption, there is clear and convincing evidence that a POSA would have been motivated to combine the '544 Patent, WO'384, and the '548 Regimen and would have had a reasonable expectation of successfully using regimens covered by the Representative Claims to treat schizophrenia.

1. The '544 Patent Enabled POSA to Administer Monthly Doses of an Aqueous Nanoparticle Suspension of Paliperidone Palmitate to Treat Schizophrenia.

The '544 Patent discloses and enables monthly administration of aqueous

nanoparticle paliperidone palmitate formulations to effectively treat schizophrenia. *Amgen*, 314 F.3d at 1354–55. The injectable formulations are, in fact, composed of "very old excipients," to produce formulations with a preferred pH of 7-7.5 that can be administered monthly to treat schizophrenia. (FF 146–149).

The '544 Patent also teaches that the size of the paliperidone palmitate particles significantly impacts the PK behavior of the formulation (FF 152) and that "micronized" particles are "exceptionally long-lasting" in humans. (FF 151). "Sub-micron," i.e. nanoparticles that have a surface area greater than 4 m^2/g^3 corresponding to "an average particle size of less than 2,000 nm" are therefore preferred. (FF 142, 153, 157). Accordingly, conventional "mechanical means," such as a mill, are used to reduce the raw, micronized particles to a desired nanoparticle size. (FF 154). And two of three of the specific examples, which differ in their particle size distribution based only on the amount of time they were milled, have d50 values in the range of "about 1600 nm to about 900 nm"—Formulations B and C.[4] (FF 162–163). The PK properties of these examples are functionally about the

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[3] While Dr. Sinko considers surface area and particle size as "two critical parameters" that must both be met to motivate a POSA, (Sinko Tr. 1547:3–14), nothing in the '544 Patent identifies the parameters as such.

[4] Whether or not the Formulation B falls within the claims of the '544 Patent or qualifies as a "preferred" formulation under that specification is of no moment. A POSA is taught that Formulation B is an effective option that is presumed enabled. *See Amgen*, 314 F.3d at 1354–55. Regardless, any argument from Janssen that Formulation B is not covered by claim 1 of the '544 Patent because

same in the beagle dog. (FF 164).

These formulations are intended for "intramuscular" injection. (FF 168). As discussed above, both parties' experts agree that a POSA would understand that "intramuscular" injections include "the deltoid of your arm or the gluteus in your buttocks." (FF 170). That is not surprising—the art consistently taught so. For example, Gibaldi taught that "[t]he IM injection site is usually the deltoid muscle." (FF 221). Goodman likewise teaches that an IM injection typically is in the deltoid and that the rate of absorption following injection into the deltoid is "generally" faster than injection in the gluteus. (FF 228). Not surprisingly, as early as 2005, a POSA injecting sustained release paliperidone palmitate formulations into the deltoid or gluteal muscles would be reasonable. (FF 356–358).

Any suggestion that a POSA would not have used the deltoid muscle as the injection site is meritless. Even if Dr. Sinko is correct that, for long-acting suspensions, the deltoid may not lead to more rapid absorption than the gluteus, (FF 230), that does not mean a POSA would not select the deltoid muscle for injecting the IS formulation. Specifically, Dr. Sinko *agrees* that a POSA understood that the deltoid and gluteal muscles are the two available options and that they would work similarly for long-acting suspensions. (FF 231, 356). Dr. Sinko also confessed he

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the d90 ≥ 2000 nm is belied by their representations that claim 7 covers IS FF 440–442), which has a d90 of 2000-4400 nm. (FF 530).

was unaware that deltoid injections are often preferred by patients for many reasons, as Dr. Wermeling, and psychiatrists Drs. Kahn, Kohler, and Gopal all testified. (FF 355). In the face of this uncontroverted evidence, any assertion that a POSA would not have been motivated to inject aqueous nanoparticle suspensions into the deltoid muscle with a reasonable expectation of success is baseless.

The '544 Patent also teaches dosing the IM paliperidone palmitate formulations at "about 2 to 4 mg/kg body weight," which, for some human subjects with a normal body weight, would be 75-150 mg-eq. (FF 174–175). The goal of this dose range is to bring patients into the "therapeutic window" of 10-100 ng/mL paliperidone—the blood plasma concentration range that is generally associated with efficacy, but not severe side effects—to treat schizophrenia.[5] (FF 177).

In sum, the '544 Patent enabled a POSA (1) to make and use a sustained release paliperidone palmitate formulation having average particle sizes in the range of about 900 nm to 1380 nm to treat schizophrenia with (2) monthly injections (3) into the deltoid or gluteal muscles, (4) in doses including at least 75-150 mg-eq.

2. WO'384 Taught an Improved Paliperidone Palmitate

[5] While Dr. Sinko opined that the '544 Patent teaches only individualized, weight-based dosing, (Sinko Tr. 2099:7–11), the Representative Claims do not require anything different (CL 62). Moreover, Dr. Sinko agreed that the '544 Patent teaches the claimed doses of 75-150 mg eq are effective for some patients. (FF 175).

Formulation Having All Ingredients of Claims 20 and 21

The WO'384 advanced the '544 Patent's teachings. The invention described in WO'384 was spurred because the sterilization method taught by the '544 Patent (gamma irradiation) caused the breakdown of paliperidone palmitate into toxic byproducts. (FF 197–199). To avoid this, WO'384 suggested a refined sterilization process replacing radiation with aseptic filters as part of "a new method of preparing the [paliperidone palmitate] product" while managing particle size. (FF 198). The WO'384 also taught a refined formulation and specific dose amounts for administration to patients as needed. In particular, WO'384 taught a specific sustained release paliperidone palmitate aqueous formulation comprising 156 mg/mL paliperidone palmitate (FF 193), intended for intramuscular (i.e., deltoid or gluteal) injection. (FF 189.) This formulation corresponds to IS, and has the exact ingredients, concentrations, and pH as claims 20 and 21 of the '906 Patent. (FF 193–195, 207–208).

A POSA would have known the WO'384 formulation was an improvement over the '544 Patent formulation. Not only was WO'384 published after the '544 Patent, but it expressly called out the European equivalent of the '544 Patent as a "suitable" prior art formulation that WO'384 was intending to improve. (FF 183, 185). Moreover, WO'384 sought to improve the '544 Patent's use of (1) gamma irradiation by introducing a new filtration process, and (2) benzyl alcohol, which

was disfavored by the FDA, by using citric acid as a preservative instead. (FF 191–192, 197–198). Because WO'384 made no new disclosure on particle size, a POSA would have known to mill the refined WO'384 formulation to have a d50 particle size between 740 nm and 1380 nm as taught by the '544 Patent Examples. (FF 202).

Finally, WO'384 further narrowed the range of dose amounts taught by the '544 Patent. Rather than a general, weight-based dosing range, WO'384 taught that syringes for injection are filled with 0.25-1.50 mL of the formulation, corresponding to doses of 25-150 mq-eq. paliperidone—the exact doses claimed in the '906 Patent. (FF 193, 205–206).

3. The '548 Regimen Taught Initiating Treatment with Loading Doses on Days 1 and 8 at Both 150 and 100 mg-eq.

Although the '544 Patent and WO'384 each teach aqueous paliperidone palmitate nanoparticle formulations suitable for monthly administration, a POSA would recognize that treatments through monthly dosing could be improved with use of loading doses. The '548 Regimen provided guidance on using loading doses followed by monthly administration of paliperidone palmitate. (FF 209–219). In particular, the '548 Regimen taught "loading doses on Days 1 and 8, followed by monthly dosing" thereafter. (FF 217–218). This protocol was published on the NIH "ClinicalTrials.gov" site, which is routinely relied upon by POSA. (FF 209–210).

A POSA would have looked to such a regimen for initiating treatment of schizophrenia. As of 2007, a POSA would have known that providing monthly

administrations alone could require about "four to five half-lives to get to steady state." (FF 321). Thus, a patient may have sub-therapeutic plasma levels after the first few injections, increasing the risk of relapse. (FF 243, 321). But a POSA also would have known that "loading doses" of the monthly formulation to initiate treatment was the preferred approach to mitigating this risk. (FF 336–338).

Loading doses were a well-known, and routine technique to achieve therapeutic plasma levels rapidly. (FF 335). For instance, two Ereshefsky articles published in 1990 and 1993 discuss the benefits of using a loading dose strategy for haloperidol decanoate, another Janssen long-acting, monthly injectable antipsychotic. (FF 68, 234, 240, 250–253). In particular, Ereshefsky 1990 promotes loading doses because "[r]apid stabilization on depot antipsychotic can reduce the length of stay for acute inpatients, as well as decrease the recidivism rate, and decrease the total cost of care." (FF 241). In contrast, "nonloading-dose, dosing regimens often require overlap of oral antipsychotic, resulting in an extended period of stabilization and possibly increased extrapyramidal side effects." (*Id.*). Ereshefsky's 1993 article likewise noted that when converting patients from oral antipsychotics to injectables, "plasma concentrations can drop significantly," which "can lead to increased risk of relapse." (FF 249). Using "a loading-dose paradigm," however, "reduce[s] the risk of relapse." (*Id.*) Ershefsky was not alone in advocating loading doses. Another prior art reference—Karagianis—says they were a

"commonly used treatment paradigm" for antipsychotics, and discusses the benefits of using a loading dose strategy for another second-generation oral antipsychotic drug, olanzapine. (FF 258–260). Hence, a POSA would have been motivated to develop loading dose regimens for the monthly formulations enabled by the '544 Patent and WO384 to avoid oral supplementation, reach therapeutic plasma levels faster, and reduce the risk of relapse. A POSA would also have been motivated to look to the known loading dose regimens for paliperidone palmitate taught by the '548 Regimen.

A POSA would have understood that, being a Phase III trial, the '548 Regimen was confirming the safety and efficacy of paliperidone palmitate doses previously tested in Phase I or Phase II trials, and therefore would have expected those doses to be reasonably safe and effective for treating schizophrenia. (FF 216, 347). Phase III trials do not typically employ regimens without an expectation of safety and treatment success. (FF 216). The reasonableness of the '548 Regimen would have been affirmed by the dose range disclosed in WO'384, which fully encompassed the doses under examination in the '548 Regimen. (FF 193, 205–206, 217, 310–312). And a POSA would have looked to the '548 Regimen as a way to administer the formulations described in the '544 Patent and WO'384, because all three references (1) concern the treatment of schizophrenia with monthly paliperidone palmitate formulations and (2) share ties to Janssen or its parent company Johnson & Johnson.

(FF 139, 180, 212, 340).

While the '548 Regimen used gluteal injections, a POSA would not have been dissuaded from deltoid injections, consistent with at least the '544 Patent, WO'384, Gibaldi, and Goodman. The '548 Regimen protocol was set to show "that the 3 fixed doses of paliperidone are each more efficacious than placebo in treating subjects with schizophrenia." (FF 219). A POSA would have expected that the regimen could also be performed with deltoid injections. (FF 356–359).

In sum, the '548 Regimen taught that a monthly formulation of paliperidone palmitate may be administered as loading doses on Days 1 and 8, followed by monthly injections on at least Days 36 and 64, and using dose amounts between 50-150 mg-eq.

4. Claim 2 Would Have Been Obvious In View of the '544 Patent, WO'384, and '548 Regimen

In view of the teachings of the prior art as a whole, even if a presumption of obviousness did not apply, a POSA reading the '544 Patent and WO'384 in view of the '548 Regimen would have been motivated to administer the formulation of Table 6 of WO'384 as part of a dosing regimen that falls within the scope of claim 2. A POSA would have been specifically motivated to select 150 mg-eq. as the first loading dose because "a POSA would be motivated to use the maximum effective and safe dose" when first loading a patient to bring them into the therapeutic window as quickly as possible. (FF 341). A POSA would have known that any of the three

doses tested—150, 100, or 50 mg-eq.—could be chosen for the second loading dose on Day 8. (FF 343).

But there are also reasons a POSA would have specifically selected the lower 100 mg-eq. amount for the second injection as well. Ereshefsky 1993, for instance, teaches a POSA to administer large "loading dose[s] in two or more sequential injections . . . every three to seven days until the full amount is given." (FF 252). For example, Ereshefsky 1993 teaches that a patient scheduled to receive a 180 mg-eq. loading dose of haloperidol decanoate may receive 100 mg-eq. on day 1, followed by 80 mg-eq. a week later. (FF 511). Moreover, "[t]o avoid excessive accumulation of the drug and thus increased side effects, the depot dose is reduced" in subsequent loading months. (FF 252). Based on these disclosures, a POSA would administer a second dose lower than the highest available dose in order to avoid the risk of excessive accumulation of paliperidone in the blood, but would want a dose high enough to effectively load the patient. (FF 341, 344). A POSA would therefore be motivated to select the middle dose tested: 100 mg-eq. (FF 344).

A POSA would also have known to administer monthly maintenance doses of 25-150 mg-eq. on, for instance, Days 36 and 64, as taught by each of the '544 Patent, WO'384, and '548 Regimen. (FF 173, 183, 217–218, 317, 323). A POSA also would have known based on these references that all of the injections could be administered in the deltoid for convenience or proclivities of a patient. (FF 355). Stated simply, a

POSA would have been motivated to select, for example, 150/100/100/100 mg-eq. administered to the deltoid on Days 1, 8, 36, and 64, and have a reasonable expectation of success as discussed below. (FF 347, 349, 374). Because this regimen falls within the scope of claim 2, it is a species of the broader genus that is claimed, thus rendering claim 2 obvious.[6] *See Aventis Pharma Deutschland GMBH v. Lupin Ltd.*, 499 F.3d 1293, 1300 (Fed. Cir. 2007) (finding the obviousness of a narrower species rendered the broader genus obvious as well); *Oramco Corp v. Align Technology, Inc*., 498 F.3d 1307, 1319 (Fed. Cir. 2007) (same).

5. A POSA Would Have Had a Reasonable Expectation of Arriving at the 150/100 mg-eq. Loading Dose Regimen

A POSA would have had a reasonable expectation of success in selecting a dosing regimen that falls within the scope of claim 2. (FF 351). Generally, a "loading dose strategy was known to a [POSA] prior to 2007" "in the context of long-acting injectables for the treatment of schizophrenia," (Sinko Tr. 1790:23–1791:9; FF 334–37), as confirmed by at least Ereshefsky 1990 and 1993, and Karagianis, which

[6] The so-called "dosing windows" referenced by Janssen at trial are no more than another way of saying a "genus" of possible days to administer each dose. Because the '544 Patent, WO'384, and '548 Regimen render obvious administering doses on Days 1, 8, 36, and 64, a claim reciting a genus that includes those days is obvious. In any event, the evidence showed that physicians were administering paliperidone palmitate within the claimed "dosing windows" as a matter of routine practice and physician discretion absent any such instruction or guidance from Janssen. (Samtani Tr. 1444:4–1446:1; FF 378–383).

discuss successful use of loading doses with other antipsychotics. (FF 333). Indeed, Janicak would have confirmed a POSA's selection of loading doses on Days 1 and 8, as it teaches that Janssen itself was pursuing such a regimen for its monthly formulation. (FF 266–67).

A POSA would also have had a reasonable expectation of success in selecting the specific dose amounts of 150 and 100 mg-eq. for Days 1 and 8. (FF 347, 349–350). WO'384 would have confirmed that doses of 25–150 mg-eq., as taught by the '548 Regimen, were reasonable, (FF 348), and lower than the high doses taught in the '544 Patent. Additionally, POSA would view the two injections in the '548 Regimen also as a total loading dose administered on two separate days (as Ereshefsky taught). (FF 245, 252, 349). The '548 Regimen, therefore, teaches that a total loading dose between 200 mg-eq. and 300 mg-eq. in the first week is expected to be safe and effective. (FF 349). And "if 300 [mg-eq.] loading doses and 200 [mg-eq.] loading doses are stated to be safe and effective, then ergo, something in between them would be safe and effective." (*Id*.). Nothing in the art teaches that loading doses have to be split evenly; in fact, Ereshefsky did the opposite (FF 245, 252, 511).

Finally, a POSA would have known from Ereshefsky that an appropriate loading dose of haloperidol decanoate was 20 times the daily oral dose—the same multiplier used in the 2007 Haldol Label. (FF 244, 250, 511). Applying this

multiplier to paliperidone palmitate, a POSA would know that the 12 mg maximum oral dose of paliperidone would equate to a 240 mg-eq. paliperidone palmitate loading dose. (FF 350). Based on the doses from the '548 Regimen, a POSA would know that a 240 mg-eq. loading dose could be administered as 150 mg-eq. on Day 1, and 100 mg-eq. on Day 8, to provide a total of 250 mg-eq. (*Id.*). At the very least, this would have confirmed that such a loading dose would be expected to be effective. (*Id.*).

While Dr. Sinko disputed that a POSA would have been motivated to combine or modify the prior art with a reasonable expectation of success without extensive individualized PK data (Sinko Tr. 1580:2–8, 1580:9–16, 1589:13–1590:4), his testimony was not credible as he misunderstood the legal significance of the claims, prior art, and patent laws. (FF 384). First, Dr. Sinko based his opinion on the incorrect assumption that no guiding data were available to a POSA. But the file history of the '906 Patent shows that PK, safety and efficacy results from the SCH-201 study, which Dr. Gopal characterized as "fantastic," (FF 554), and which tested loading doses of 50/50 and 100/100 mg-eq. on Days 1 and 8, published in October 2007. (FF 104–05, 554).

Additionally, Dr. Sinko incorrectly assumed that to arrive at the claimed dosing regimen, a POSA must know that the dosing regimen would successfully treat a patient. (FF 385). But, although efficacy and safety data may be necessary to

create a reasonable expectation of success for the claims of some patents claiming novel treatment results, that is not the case for the '906 Patent. The claims, however, ***do not require any showing of efficacy***. (FF 386; CL 62). Instead, the plain language requires only a dosing regimen for a "patient in need of treatment," merely a desire that treatment will occur. *See, e.g.*, *Horizon Therapeutics, Inc. v. Par Pharm., Inc.*, No. 2:14-cv-00384-JRG-RSP, 2015 WL 6165427, at *10 (E.D. Tex. Oct. 20, 2015) ("The ordinary meaning of treating does not include an efficacy requirement. It requires a person of ordinary skill in the art 'treating' a patient to attempt to assist the patient."); *see also Tyco*, 642 F.3d at 1374 ("[T]he '954 claims are not tied to product efficacy, so the absence of any particularized discussion of efficacy in the BNF reference is immaterial to obviousness[.]"); *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (claims directed to "a method for the treatment or prevention of stroke or its recurrence" do not require efficacy); *Aventis Pharma S.A. v. Hospira, Inc.*, 743 F. Supp. 2d 305, 342–43 (D. Del. 2010), *aff'd*, 675 F.3d 1324 (Fed. Cir. 2012) (where "safety[ ] and efficacy are not requirements of the asserted claims," a defendant need not prove "'a reasonable expectation of success' with respect to . . . safety[or] efficacy"). In any event, the law "has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness,'" *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018), because "[a]ll that is required is a reasonable expectation of success." *Hoffmann-La Roche Inc. v. Apotex*

Inc., 748 F.3d 1326, 1331 (Fed. Cir. 2014).

Moreover, a POSA would have known that being a Phase III trial, the '548 Regimen indicated loading doses between 50-150 mg-eq. were expected to be reasonably safe and effective for administering to subjects with schizophrenia. (FF 216); *see Montgomery*, 677 F.3d at 1382 ("HOPE's protocol for the administration of ramipril is far from an abstract theory—it is an advanced stage of testing designed to secure regulatory approval. . . . HOPE's authors could have obtained the patent claims at issue based [on] the HOPE reference, so it cannot be that this reference fails to anticipate."). And a POSA would have been affirmed in this view based on WO'384's disclosure of a dose range of 25-150 mg-eq. (FF 348). As such, a POSA would not need extensive, individualized PK data to have a reasonable expectation of treating a schizophrenia patient with a dosing regimen that falls within the scope of claim 2. (*Id*.). The '906 Patent has no data using the claimed regimens, and Janssen cannot demand more from the prior art than what the patent itself teaches. *Lockwood v. Am. Airlines, Inc.*, 107 F. 3d 1565, 1570 (Fed. Cir. 1997) (invalidating prior art need not disclose a level of detail that is not disclosed or claimed in the asserted patent itself).

Dr. Sinko also incorrectly assumed that all claims require administration of the IS formulation. (FF 391). But "[t]here is no requirement that [POSA] have a reasonable expectation of success in developing [the brand drug itself]. Rather,

[POSA] need only have a reasonable expectation of success of developing the claimed invention." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013). The plain language of claim 2 requires only "paliperidone palmitate formulated in a sustained release formulation," and claims 10 and 13 require "an aqueous nanoparticle suspension." (FF 125–27). The paliperidone palmitate formulations of the '544 Patent, even without the advances of WO'384, satisfy the formulation limitations of claims 2, 10 and 13. (FF 339). Nowhere do these claims require a formulation identical to IS, as Dr. Sinko incorrectly assumed. And the specific ingredients and concentrations recited in claim 19 (from which claims 20 and 21 depend) were disclosed exactly in WO'384. (FF 194).

6. Cleton 2008 Confirms the Obviousness of Claim 2

While the Court does not need Cleton 2008 to find the dosing regimen of claim 2 obvious, Cleton 2008 confirms it is obvious. The first study, PI-74, taught that dose amounts of a long-acting, aqueous nanoparticle suspensions of paliperidone palmitate ranging from 25-150 mg-eq. were, in fact, safe, effective, and well-tolerated by patients, whether administered in the deltoid or gluteus. (FF 290, 296). The second study, PI-75, taught that a dosing regimen of 100/100/100/100 mg-eq. administered in the deltoid on Days 1, 8, 36, and 64 was also safe, effective, and well-tolerated. (FF 299–300, 307). At bottom, Cleton 2008 provides the confirmatory data that Dr. Sinko desired (but a POSA, in fact, would not need). (FF

285). With this in mind, a POSA would have concluded with even greater confidence that a dosing regimen such as 150/100/100/100 mg-eq. administered in the deltoid on Days 1, 8, 36, and 64 would be reasonably safe and effective for a patient in need of treatment for schizophrenia.

7. The Prior Art Renders Claims 20 and 21 Obvious.

As discussed above, the manipulative steps of claim 2 would have been obvious. The additional structural limitations of claims 19, 20, and 21 do not make those claims less so. The ’544 Patent and WO’384 together taught a formulation that would meet all the structural limitations of claims 20 and 21 (which depend from claim 19), and it would have been obvious to use that formulation in the claimed dosing regimens, as discussed above. Specifically, WO’384 teaches the exact ingredients and concentrations as those found in claims 20 and 21. (FF 193–94).

A POSA would have been motivated by the ’544 Patent to produce a formulation having a d50 within the claimed range. In particular, a POSA would have known from the ’544 Patent’s Formulations B and C, 4 hours of milling produces a d50 of 1380 nm, and 7 hours of milling produces a d50 of 740 nm. (FF 155–56, 162–63). Both of these values are “about 1600 nm to about 900 nm”. (*Id*.). And because the disclosure related to preferred particle sizes in WO’384 matches that of the ’544 Patent, it would have been obvious to POSA to mill the WO’384 formulation for about 4 or 7 hours, producing a d50 of about 1380 nm and 740 nm.

(FF 200, 202).

But a POSA would not have simply replicated Formulations B and C: a "person of ordinary skill is also a person of ordinary creativity, [and] not an automaton" limited to express teachings of the prior art references. *KSR*, 550 U.S. at 420–21. There is no dispute that particle size is a "result effective variable" that impacts the PK of the formulation such as absorption and bioavailability (FF 152, 363), and it is well established that the "discovery of an optimum value of a result effective variable . . . is ordinarily within the skill of the art." *Synvina*, 904 F.3d at 1010; *see also In re Applied Materials*, 692 F.3d at 1297 (where the prior art recognizes "that a property is affected by the variable," optimization of that variable requires only ordinary skill and is not patentable). A POSA would also know that particle size is determined entirely by milling time. (FF 154–56, 166). Thus, a POSA would have been motivated to optimize the particle size disclosed by the prior art to maximize early efficacy and maintain that efficacy over the course of a month. (FF 364–65, 368). A POSA, expressing this ordinary creativity and desire to optimize a known result-effective variable, would know that formulations could be milled for any amount of time, including sometime between 4 to 7 hours. (FF 366). And a POSA would have been capable of conducting a simple PK study to test the resultant formulation's properties. (FF 165).

In sum, WO'384 and the '544 Patent would have motivated a POSA to

produce a formulation having all the ingredients and concentrations of the WO'384 formulation, having a d50 "of from about 1600 to about 900 nm," with a reasonable expectation of success.

8. The Prior Art Taught Reduced Doses for Renal Impairment

Claims 10 and 13, directed to dosing regimens for renally impaired patients, fare no better. The difference between the general dosing regimens of claim 2 and the regimens of claims 10 and 13 is that, instead of administering 150/100 mg-eq. as the loading doses, the amounts are reduced to 75/75 mg-eq. Putting aside the fact that claims 10 and 13 are also presumptively obvious over the '544 Patent, WO'384, and '548 Regimen (teaching a loading dose range encompassing 75 mg-eq. for both doses), *see Tyco*, 642 F.3d at 1372–73; *see also* Section II.A–B, a POSA would have already known, based on additional prior art, to reduce the doses for patients with renal impairment.

The '591 Application, for instance, is directed to a formulation of paliperidone palmitate and its impact on patients with hepatic (or liver) impairment. (FF 271). The specification, however, teaches that paliperidone administered as paliperidone palmitate is excreted primarily through the kidneys. (FF 272). This elimination pathway is further confirmed by Cleton 2007, which teaches that the maximum concentration of and total exposure to paliperidone "is basically doubling for patients who have renal impairment." (FF 275). Although Cleton 2007 examined the

oral form of paliperidone, a POSA would know that its teachings would apply to paliperidone palmitate, because once paliperidone palmitate is administered, "you won't be measuring paliperidone palmitate in the blood. You would simply be measuring paliperidone." (FF 80). Thus, the '591 Application and Cleton 2007, alone or in combination, teach a POSA that, for patients with renal impairment, the dose must be reduced because "it's not being removed from the body" as efficiently. (FF 371).

A POSA would also know, based on the label for oral paliperidone (Invega ER), how much to reduce the dose for patients with renal impairment. (FF 375). Specifically, the Invega ER Label teaches "maximum recommended dose[s]" of "12 mg/day" for patients with normal renal function and "6 mg/day" for patients with mild renal impairment. (FF 278–79). Thus, a POSA would read the Invega ER Label as requiring a 50% dose reduction for patients with mild renal impairment, which coincides with the approximate doubling of paliperidone plasma concentrations in such patients taught by Cleton 2007. (FF 275, 280, 375).

Dr. Sinko mistakenly compared the "recommended" (not "maximum recommended") dose of 6 mg/day for patients with normal renal function to the "maximum recommended" dose of 6 mg/day for patients with mild renal impairment. (Sinko Tr. 1587:9–1588:6). Even assuming POSA would make the same erroneous comparison, the Invega ER Label also teaches that the "maximum

recommended" dose of Invega ER for patients with moderate or severe renal impairment is "3 mg," which is a 50% dose reduction of the "recommended" (but not "maximum recommended") dose for patients with normal renal function. (FF 281). Either way, some level of renal impairment requires a 50% dose reduction.

Based on the doses and dose ranges taught by the '544 Patent, WO'384, and the '548 Regimen, and reducing these doses by 50% for patients with some degree of renal impairment, POSA would have reasonably selected loading doses of 75/75, 75/50, or 75/25 mg-eq. and subsequent maintenance doses between 25–75 mg-eq. for patients with varying degrees of renal impairment. (FF 343, 345, 374–376). Therefore, a POSA would have found obvious at least the dosing regimen of 75/75/50/50 in the deltoid on Days 1, 8, 36, and 64 for patients with renal impairment, (FF 376), which renders claims 10 and 13 obvious. *See Aventis Pharma*, 499 F.3d at 1300; *Oramco Corp.*, 498 F.3d at 1319.

Finally, to the extent Janssen argues that "of from about 75 mg-eq." in claims 10 and 13 encompasses doses up to 150 mg-eq., (FF 664), these claims are encompassed at least by the '548 Regimen. (FF 309–313).

9. The '906 Patent Is Not Entitled To a Priority Filing Date of December 19, 2007

"[A] patent's claims are not entitled to an earlier priority date merely because the patentee claims priority." *In re NTP, Inc.*, 654 F.3d 1268, 1276 (Fed. Cir. 2011). "[T]o gain the benefit of the filing date of an earlier application . . . each application

in the chain leading back to the earlier application must comply with the written description requirement." *Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378 (Fed. Cir. 2007). ***Janssen*** bears the burden of proving that it is entitled to claim priority to the filing date of an earlier application. *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1303–06 (Fed. Cir. 2008).

The relevant question is whether the '918 Provisional within its four corners demonstrates that the inventors possessed the full scope of the dosing regimens they later claimed in the '906 Patent. Janssen made no such showing. Its main prior art expert, Dr. Sinko, expressly said that he did not analyze issues of priority. (Sinko Tr. 1590:15–21, 1591:2–8). Indeed, no witness pointed to any working example of an embodiment of any of the claims that were eventually granted in the '906 Patent—because there is none. Nor does the '918 Provisional disclosure satisfy written description for any of the Representative Claims. For example, the '906 claims recite administering an injection "monthly (±7 days)," (or Days 27-48 (FF 123)), but neither the words "monthly (±7 days)" nor any equivalent concept appears anywhere in the '918 Provisional. No evidence of record establishes that the '918 Provisional application conveys to a POSA that the inventors were in possession of a dosing regimen allowing for the administration of a maintenance dose on Days 27-48. Similarly, claims 20 and 21 (depending from claim 19), recite average particle size of "about 1600 nm to about 900 nm." That range is not described in the '918

Provisional. (FF 135). Accordingly, Janssen has failed to meet its burden of showing that the '906 Patent is entitled to a filing date of December 19, 2007.

10. Cleton 2008 Is Not Disqualified As Prior Art Under *Stryker*

In the PTO, Janssen cited *In re Stryker*, 435 F.2d 1340 (C.C.P.A. 1971), to argue that Cleton 2008 is not prior art. To the extent that Janssen interprets *Stryker* to hold that to have a reference removed as prior art, a patentee is required to show possession of only so much as is shown by the reference, Janssen is wrong. *See In re Dardick*, 496 F.2d 1274, 1240 (C.C.P.A. 1974). Rather, *Stryker* merely found an affidavit sufficient to antedate a reference because the reference sought to be removed as prior art and the earlier conception sworn to in the affidavit were both insignificantly different from the subject claim. *Stryker*, 435 F.2d at 1341–42. But here, there is simply no evidence Dr. Vermulen and Dr. Wouters conceived of the later-claimed invention prior to Cleton 2008 publication. The '918 Provisional application is certainly not parallel to the affidavit evidence in *Stryker*. Dr. Vermeulen herself testified it does not disclose the complete invention. (Verm. Tr. 919:20–920:17; FF 133–35, 107) Accordingly, the fact that something resembling the disclosure of Cleton 2008 may have been included in the '918 Provisional does not disqualify it as prior art.

11. Janssen Has Not Proven An Invention Date Prior To December 19, 2007

Finally, despite Janssen's assurances that Drs. Vermeulen, Gopal, and

Samtani's testimony would establish an invention date prior to December 19, 2007 by six joint inventors, the evidence at trial was to the contrary.

"[A]n inventor can swear behind a reference by proving he conceived his invention before the effective filing date of the reference and was diligent in reducing his invention to practice after that date." *Apator Miitors ApS v. Kamstrup A/S*, 887 F. 3d 1293, 1295 (Fed. Cir. 2018). Conception is "the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Burroughs Wellcome Co. v. Barr Labs., Inc.,* 40 F.3d at 1223, 1228 (Fed. Cir. 1994). "An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." *Id.* Conception must include every feature of the claimed invention, and is complete "only when the idea is so clearly defined in the inventor's mind ***that only ordinary skill would be necessary to reduce the invention to practice***, without extensive research or experimentation." *Id.* (emphasis added). In fact, "[i]t is settled that in establishing conception, a party ***must show possession of every feature recited in the count***, and that ***every limitation of the count must have been known to the inventor*** at the time of the alleged conception." *James v. J2 Cloud Servs., LLC*, 823 F. App'x 945, 949 (Fed. Cir. 2020) (emphases added). Moreover, "when a party seeks to prove conception through an inventor's testimony, the party must proffer evidence, in

addition to [the inventor's] own statements and documents, corroborating the inventor's testimony." *Apator*, 887 F.3d at 1295. "Even the most credible inventor testimony is a fortiori required to be corroborated by independent evidence." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171–72 (Fed. Cir. 2006).

None of the named or alleged inventors explained how and when they jointly were in possession of a "definite and permanent idea of the complete and operative invention [such that] only ordinary skill would be necessary to reduce the invention to practice." *Burroughs Wellcome*, 40 F.3d at 1228. To the contrary, a month before filing the '918 Provisional, Janssen sought FDA approval for ***a different dosing regimen*** than the one claimed. (FF 92). And over six months later, ***in June 2008***, at Janssen "the obvious question" still was "which was better": the claimed "150/100" regimen, "or the 100/100 dosing regimen" which Janssen had submitted to the FDA shortly before it filed the '918 Provisional. (FF 675). Accordingly, Janssen has failed to meet its burden of showing the inventors conceived of the claimed invention before the publication of Cleton 2008 and were diligent in reducing the invention to practice. Faced with ***no evidence*** to the contrary, the Court should therefore find that Cleton 2008 is prior art to the '906 patent.

The Court should also decline Jansen's invitation to "correct" the inventorship of the '906 Patent. In the PTO, Janssen asserted that An Vermeulen, Alfons Wouters, Srihari Gopal, Peter Lewyn-Briscoe, Mahesh Samtani, and Vivek Kusumakar are all

joint inventors of the '906 Patent. (D.I. 133 at 14). No evidence at trial supported such an assertion. As an initial matter, no evidence or testimony was presented about any purported contribution by Drs. Kusumakar and Lewyn-Briscoe. Dr. Wouters' purported contribution to the claimed invention is likewise unclear. While Dr. Vermeulen testified he was the formulator "overall responsible for the formulation," she was unaware of any specific contribution to the formulation in the '906 Patent, (Verm. Tr. 846:20–847:2), and the evidence shows he is not named as an inventor on any of the paliperidone palmitate formulation patents or applications owned by Janssen—WO'384, the '544 Patent, and the '843 Patent. (FF 140, 181, 843). Moreover, Dr. Vermeulen made clear that "tens of people" contributed to the invention, and no one person's contribution was more significant than others. (FF 668). Far from establishing that the six individuals asserted by Janssen are joint inventors of the '906 Patent, Janssen has, at best, shown that if these six individuals are inventors, so are numerous other individuals who had significant contributions to the invention.

Two days before this submission was due, Janssen ***for the first time*** informed Teva that it will now ask the Court to correct inventorship only as to Drs. Gopal and Samtani. This appears nowhere in the PTO and is contrary to Janssen's prior representations and sworn affidavits to the Court and PTO. (D.I. 91; DTX-2.1693–1700/PTX-2). For the same reasons discussed above, this theory too must fail.

D. Secondary Considerations Do Not Overcome the Strong Prima Facie Case of Obviousness

The Court should hold the '906 Patent claims invalid for obviousness because Janssen has not come forward with persuasive evidence that "(1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma*, 737 F.3d at 738.

At trial, Janssen focused on commercial success, copying, industry praise, and [redacted] (FF 403–05). But Janssen's evidence is too weak to overcome the presumption of obviousness or Teva's strong showing that a POSA would have been motivated to use the claimed subject matter with a reasonable expectation of successfully treating a patient with schizophrenia. [redacted], and Janssen has failed to show any relationship between its alleged secondary considerations and the merits the claimed inventions or that such evidence is commensurate with the scope of the claims. *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013) ("For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention."); *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims."). In other words, if the secondary consideration "is due to an element in the

prior art, no nexus exists." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011); *Kao*, 639 F.3d at 1068. Janssen's objective evidence fails, as it must, because the '906 Patent improperly claims what was already patented by Janssen and known to a POSA from the prior art.

1. There Was No Copying

The only evidence of purported copying that Janssen identified was the development of Teva's ANDA. But courts have recognized that "evidence of copying in the ANDA context is not probative of nonobviousness," *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013), because "the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects." *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, No. IP 02-0512, 2004 WL 1724632, at *38, n. 21 (S.D. Ind., July 29, 2004). Federal regulations require that generic versions of injectable drugs share many characteristics with the branded reference product. (FF 526; CL 94). Copying these characteristics has no bearing on the obviousness of underlying patents.

Recognizing the shortcomings of its argument, Janssen presented a brand new theory for the first at trial, [redacted] (Sinko Tr. 1625:1–6). But even if that were true, Teva's purported copying has nothing to do with the obviousness of the '906 Patent claims. (FF 531).

As both parties' experts agree, federal regulations require that generic injectable drugs be both qualitatively (Q1) and quantitatively (Q2) the same as the reference drug, meaning that Teva's generic must have the same ingredients (Q1) in the same amounts (Q2) as IS. (FF 526; CL 94). At trial, however, Dr. Sinko opined that federal regulations [redacted]

Yet Dr. Sinko was unaware that before Teva had filed its ANDA, Janssen submitted a Citizen's Petition to the FDA seeking a heightened bioequivalence standard that, if granted, would serve to implicitly regulate the particle size of Teva's ANDA product.[7] (FF 529; *see also* FF 525–28; CL 94–95). Faced with Janssen's public request that the FDA not approve generic formulations with a different particle size, it is not surprising that in an ANDA filed over 4 years later, [redacted] (FF 530). Teva's choice is in no way probative of nonobviousness. *Aventis Pharma Deutschland v. Lupin, Ltd.*, No. 2:05 CV 421, 2006 WL 2008962, at *45 (E.D. Va

[7] Being the only expert who testified about any purported copying, Dr. Sinko's lack of awareness of Janssen's Citizens Petition (in spite of being cited in Dr. Wermeling's expert report, which Dr. Sinko reviewed) renders his opinion on copying unreliable, and should be given no weight. *See, e.g.*, *Madden v. U.S. Dep't Veterans Affairs*, 873 F.3d 971, 974 (7th Cir. 2017) (finding no error in district court determination that expert witness was not credible where his "testimony proved, if nothing else, his lack of knowledge and familiarity" with the issues in the case).

July 17, 2006) ("[The copying] rationale is considerably weakened . . . by the fact that there are various other reasons why an invention may have been copied."). Moreover, [redacted]. For evidence of copying to be probative, "more is needed than merely showing that similarity exists between the patent and the competitor's accused product." *Liqwd, Inc. v. L'Oreal USA Inc.*, 941 F.3d 1133, 1137 (Fed. Cir. 2019).

2. There Was No Failure of Others

Like copying, Janssen only pointed to Teva's ANDA as evidence of "failure of others." (FF 532). In particular, [redacted] (*See* PTX-44; FF 534). While "[e]vidence that others tried but failed to develop ***the claimed invention***," *In re Cyclobenzaprine Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012) (emphasis added), or "to find a solution ***to the problem which the patent[ ] in question purport[s] to solve***," *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578–79 (Fed. Cir. 1991) (emphasis added), may be relevant to

[8] Ironically, Janssen argues that Teva copied Janssen's product, but allegedly also "failed". But if Teva copied Janssen's patented formulation and still "failed," that would indicate that the '906 Patent is not enabled rather than that it is not obvious.

nonobviousness, there is no such evidence here. Indeed, there is ***no evidence*** that Teva ever failed to administer the claimed dosing regimen or failed to create a formulation that falls within the scope of the claims. (FF 533). To the contrary, the evidence shows the claimed regimen could be practiced routinely with Teva's ANDA product and IS. (FF 533). In fact, Janssen seeks a judgment of infringement from the Court because it recognizes [redacted]. (FF 535). That should be the end of the inquiry.

Instead, Janssen's evidence merely shows [redacted] Such facts have no bearing on the obviousness of the '906 Patent.[9] [redacted]. *Cf. Hoffmann-La Roche*, 748 F.3d at 1330 ("failure to generate statistically significant results points to a fault in the study," not non-obviousness).

[9] [redacted]

3. There is No Evidence of Industry Praise

There is also no evidence of industry praise for Janssen's purported invention claimed in the '906 Patent. Indeed, all Janssen offered to support alleged praise was testimony from Dr. Gopal that Janssen may have nominated itself for an award that it did not win, an FDA presentation allegedly praising Janssen's PK modeling efforts, and two articles sponsored by Janssen that bear no relevance to the '906 Patent claims.

To support a finding of nonobviousness, "[i]ndustry praise must . . . be linked to the patented invention." *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010). However, "bare journal citations and self-referential commendation fall well short of demonstrating true industry praise. Furthermore, industry praise of what was clearly rendered obvious by published references is not a persuasive secondary consideration." *Bayer*, 713 F.3d at 1377.

First, Dr. Gopal testified, without offering any documentary support, that IS "was nominated" for but did not win the Prix Galien Award. (FF 614). Even if a mere nomination for an award were sufficient (it is not), without any showing of how that award is tied to the merits of the claimed invention, it cannot in any way bear on the alleged nonobviousness. *See S. Alabama Med. Sci. Found. v. Gnosis S.P.A.*, 808 F.3d 823, 827 (Fed. Cir. 2015) (finding no nexus to the novel features of the claimed invention because "the praise was particularly directed to the use of [ ]

an element already known in the prior art," and the award "touted" by the patentee was for the prior art ingredient); *cf. Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1333 (Fed. Cir. 2019) (finding evidence of industry praise when the awards specifically commended the novel features of the claimed invention). Here, Dr. Gopal did not know why or how IS was nominated for the award, and, in fact, it is possible Janssen nominated itself. (FF 614). At bottom, there is no evidence linking the nomination to the purported merits of the claimed invention.

Second, Janssen offered a slide deck purportedly created by an FDA employee—which plainly does not reflect the actual views of the FDA.[10] (FF 615). Janssen elicited no testimony about the contents of this document, and any possible praise in this document would relate only to Janssen's modeling work. (*Id.*). The '906 Patent, however, does not disclose or claim a new method of modeling clinical PK; it claims only a dosing regimen, which the presentation does not discuss.

Third, Janssen pointed to Einarson to purportedly establish that IS led to reduced healthcare costs and increased QALYs. (*See* PTX-134). But Einarson used aggregated data from multiple studies, including studies that did not follow the claimed regimen, to arrive at his conclusions, undermining any notion that these alleged improvements are due to the ***claimed*** dosing regimen. (FF 616).

[10] Any statement made therein is hearsay and cannot be used to prove the truth of the matter asserted. Fed. R. Evid. 801–803.

Additionally, while the paper concluded that IS reduced costs for the ***Czech Republic*** healthcare system, as Dr. Kahn testified, "that's extremely difficult to extrapolate to the U.S. situation because of price" differences in the two countries. (Kahn Tr. 2325:3–25; FF 619). Lastly, Einarson showed that IS provided a 2–3 additional days of healthy life, Dr. Kahn explained that is not clinically significant. (FF 620). The article also fails to link this minimal increase in QALYs to the merits of the claimed invention; it is thus not probative of non-obviousness.

Finally, Janssen relied on Emsley, but that article concedes that "[t]here was no statistically significant difference in the rate of efficacy failure of [IS] compared with haloperidol decanoate," and that IS led to serious metabolic side effects and "higher average costs for inpatient and outpatient services and medication" for IS compared to haloperidol decanoate. (FF 622). In addition to explaining the pitfalls of IS, Emsley also notes that he had received funding from Janssen. (FF 623). Similarly, although Janssen also points to the Lawrence Supplements as evidence of praise, "Janssen was involved in the outline development and medico-legal approval" of the article, "and provided financial support for its publication." (PTX-506 at 7–8, FF 624). Such self-serving press, even if relevant, does not support a finding of non-obviousness. *See, e.g.*, *Amarin Pharma, Inc. v. Hikma Pharm. USA Inc.*, 449 F. Supp. 3d 967, 998 (D. Nev.), *aff'd*, 819 F. App'x 932 (Fed. Cir. 2020) (rejecting patentee-sponsored articles of purported praise).

4. There Was No Skepticism

Janssen offers two alleged sources of skepticism: (1) the interpretation of Janssen's fact witnesses of the supposed thoughts and beliefs of confidential advisors; and (2) the FDA's initial Complete Response Letter suggesting additional dosing regimen options ***other than the one claimed***. Try as Janssen may to reshape the narrative, this simply is not evidence of skepticism.

As to the first allegation, leaving aside the fact that every statement concerning the alleged skepticism of Janssen's advisors or individuals in the medical community is inadmissible hearsay, FRE 801–803,[11] no statement actually evidences skepticism that the claimed dosing regimen could be used to treat schizophrenia. Rather, Dr. Gopal offered testimony that certain Janssen advisors "didn't believe that [Janssen] would get FDA approval" of its desired 150/100 mg-eq. regimen, without running a clinical trial on it, and that "[t]hey thought it was

[11] What Janssen's advisors or medical professionals thought or said out of court is hearsay if used as evidence of actual skepticism. *See Allergan, Inc. v. Watson Labs., Inc.-Fla.*, 869 F. Supp. 3d 456, 490 (D. Del. 2012), *aff'd*, 470 F. App'x 903 (Fed. Cir. 2012) (rejecting plaintiffs' skepticism argument where "no written or published statements of skepticism . . . were introduced into evidence," and the testimony "refer[red] only to out-of-court statements of unnamed . . . employees" of another pharmaceutical company). While Janssen tried to circumvent this evidentiary hurdle by asking the witnesses their "understanding" of these statements, such testimony may only be used to prove the witness's state of mind, not actual skepticism. *See United States v. Sotelo*, 707 F. App'x 77, 85 (3d Cir. 2017) ("Statements from third parties . . . were not introduced for the truth of the matter, but rather to show the effect on [the witness].").

actually risky" to file an NDA without having the trial data. (Gopal Tr. 1075:13–16; 1079:7–11, 1080:5-12, 19–23). Dr. Samtani similarly testified that "the advisors were, in general, skeptical about using population PK modeling for designing dosing recommendations for paliperidone palmitate that had not been studied in these pivotal clinical studies." (Samtani Tr. 1347:16–1348:10). But whether Janssen's advisors thought Janssen could obtain regulatory approval for its proposed dosing regimen (based on population PK modeling or other data) has only to do with whether Janssen had the right kind of data to present to the FDA and not with the alleged non-obviousness of the claimed invention.

As for the FDA's addition of a 75 mg-eq. dose to the draft IS label, that too does not evidence skepticism. Statements from the FDA that "reflect[ ] attention to the FDA's normal duties ensuring the safety and efficacy of new drugs" does not rise to the level of skepticism for purposes of non-obviousness. *See Bayer*, 713 F.3d at 1377. In that case, "[a]s evidence of expert skepticism, Bayer cite[d] an FDA request for clinical safety data and data demonstrating efficacy benefits sufficient to justify the added synthetic hormone exposure required for the proposed 24/4 dosing regimen." *Id*. But the Federal Circuit concluded "[t]hat request in no way indicates that FDA experts would have been surprised to receive such data." *Id*.

Likewise here. The FDA's addition of a lower dose option is not skepticism, but rather "advice to explore a lower dose." (FF 610). There was no statement

accompanying the FDA's recommendation that it considered 100 mg-eq. too high. (*See* PTX-94). Nor was "the 100 [mg-eq. dose] . . . struck out," meaning that the "physicians had the opportunity to choose between the two doses [of 75 or 100 mg-eq.] for both the first and second injection." (Gopal Tr. 1210:11–14; FF 610). Indeed, after Janssen formally applied for the 150 mg-eq. dose, the FDA approved it without any apparent pushback. (FF 97). The FDA correspondence as a whole, actually evidences obviousness; the claimed regimen is so insignificantly different from all the other loading dose regimen studies conducted, the FDA did not require it to be run in any Phase III trials to approve it. The differences are not critical.

5. There Were No Unexpected Results

None of Janssen's experts opined on unexpected results. (FF 539). "In order to properly evaluate whether a superior property was unexpected, the court [must] consider[] what properties were expected." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Moreover, "the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991); *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (same). At trial, none of Janssen's experts testified as to what a POSA would have expected of the claimed dosing regimen, let alone how those expectations would compare to any of the dosing regimens of the '544 Patent, WO'384, or the '548 Regimen. This is dispositive of the unexpected results inquiry.

Rather than provide any evidence of unexpected results arising from differences between the claimed dosing regimen and the closest prior art, Janssen focused on its own missteps on the road to regulatory approval. Janssen provided no expert testimony that the inventors' mistakes are ones that a POSA would have made; indeed, they are not, as discussed below. Thus, the testimony of Janssen's tribulations are not probative of nonobviousness of the claimed invention ***to a POSA***. Ironically, Janssen themselves want to rely on the inventors' struggles to show nonobviousness, but "the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000). In any event, Teva does not dispute the lengths Janssen went through to obtain FDA approval, but "[u]nsupported statements by the inventors, including in the specification, 'cannot support a finding of unexpected results.'" *Pernix Ir. Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 617 n.15 (D. Del. 2018), *aff'd sub nom. Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019) (quoting *Tyco*, 642 F.3d at 1377). Such testimony "is less compelling, coming as it does from persons with an interest in the validity of the patent." *Pernix Ir.*, 323 F. Supp. 3d at 617 n.15.

Moreover, the alleged difficulties Janssen faced during development were avoidable. For instance, Dr. Gopal alleged that several clinical studies "failed" or

were "disasters" due to an unexpected BMI effect.[12] (FF 563). Setting aside the fact that the studies did not fail—they largely met their efficacy endpoints as represented in the FDA-approved IS Label—the record shows that these results should have come as no surprise. (FF 590). For instance, in its Phase III trials, Janssen had used a 1.5-inch needle for all injections into the gluteal muscle, despite Gibaldi's teaching to ensure a long enough needle length, and having taught in the '544 Patent that a 2-inch needle should be used in some instances. (FF 600, 220, 171). And they made this choice despite knowing, as early as 2005, that the average thickness of the fat tissue in the gluteal exceeded the length of the 1.5-inch needle, which means "that the drug might have been partly administered in the adipose instead of the muscle tissue when injected in the gluteal muscle." (PTX-181 at 84; FF 601).

Janssen's early clinical studies succeeded with a 1.5-inch needle because, in those studies, a BMI cap excluded morbidly obese patients from participating. (FF 592). Yet for its Phase III trials, PSY-3002, PSY-3003, and PSY-3004, Janssen elected to administer all injections in the gluteal muscle, without including the BMI cap from the earlier studies. (FF 592). Thus, for the first time, Janssen was testing

[12] A second avoidable error that is not probative of nonobviousness was caused by a computer programming error that mixed up subjects who were to receive 150 mg-eq. injections, making that data unusable. (FF 559–60). The subjects who successfully received 100 mg-eq. injections, though, showed statistically superior improvement in that same study (FF 558)

its dosing regimen in morbidly obese patients, with a needle that a POSA would have expected to be too short to reach the gluteal muscle for these subjects. (*Id*.). Unsurprisingly, in the PSY-3002 study, paliperidone palmitate performed nearly identically to Risperdal Consta for all but the most obese subjects. (FF 602). And, unsurprisingly, Risperdal Consta—which used a 2-inch needle—did not suffer from the same BMI effect in morbidly obese patients. (FF 603). Because ultimately Janssen explained to the FDA that so-called failed results were caused by the 1.5-inch needle length (FF 597), here the Court should find the problems Janssen experienced are not probative of non-obviousness.

Realizing its error too late, Janssen was forced to find a work-around. Janssen employees recognized that including a 2-inch needle would be a "nightmare" and would "require starting the technical development all over again." (FF 604). Instead of starting all over again, Janssen required the first two injections be given in the deltoid—a muscle surrounded by less fat tissue—and increased the dose for all patients to ensure that even if not all the paliperidone palmitate quickly made it into the muscle of the obese patients with a 1.5-inch needle, enough would. (FF 605–06). Recognizing that the problem was none other than access to the muscle tissue, Janssen recommended two different needle lengths for the deltoid based on body weight—1" and 1.5". (FF 606). Janssen could have done the same for the gluteal muscle, but it would have had to begin development "all over again." (FF 604). Not

surprisingly, Janssen elected not to do that.

Janssen ultimately selected a dosing regimen from many available (and publicly disclosed) options, for its own commercial reasons. (FF 591). While Janssen may have spent significant time and resources supporting the regulatory approval of this regimen, those efforts have no relevance to the obviousness of the '906 Patent and do not entitle Janssen to "withdraw[] what already is known into the field of its monopoly and [to] diminish[] the resources available to skillful men." *KSR*, 550 U.S. at 416.

6. Janssen Has Failed To Show Nexus

Regardless of which secondary consideration it ultimately alleges, Janssen has failed to prove that "a nexus [] exist[s] between the evidence and the merits of the claimed invention." *Novartis AG v Torrent Pharms., Ltd.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017). Because, as shown above, the claimed regimen is not used with IS the majority of the time, Janssen's "secondary consideration[s] actually result[ ] from something other than what is both claimed and novel in the claim, [so] there is no nexus to the merits of the claimed invention." *In re Kao*, 639 F.3d at 1068.

A "nexus is only presumed when the product tied to the evidence of secondary considerations ***is*** the invention disclosed and claimed." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1374 (Fed. Cir. 2019). Janssen represented to the FDA that IS embodies not only the '906 Patent, but at least three other patents it listed in the

Orange Book and which are all prior art to the '906 Patent. (FF 416). Where, as here, "a product embodies claims from [multiple] patents, a presumption of nexus can be appropriate ***only if the claims of [all] patents generally cover the same invention***," *Fox Factory*, 944 F.3d at 1375, which Janssen contests.

Moreover, Janssen did not offer any evidence that IS is an embodiment of claims 10 and 13, simply because IS does not practice those claims. The IS Label recommends that patients with mild renal impairment receive a first loading dose of 100 mg-eq. and a second loading dose of 75 mg-eq, (FF 87), whereas the claims of the '906 Patent require that both doses be "of from about 75 mg-eq." (SF 9 at cl. 10, 13). As such, Janssen cannot show a nexus between any secondary consideration and the dosing regimens of claims 10 and 13. (FF 406–08).

The record is also devoid of any evidence that the alleged secondary considerations are commensurate in scope with the '906 Patent claims, or that any nexus is attributable to the combination of a purportedly novel combinations of prior art elements. *See Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016) (finding nexus must be tied to the novel features of a combination of prior art elements, not unclaimed features or prior art feature in isolation). As such, none of Janssen's purported secondary considerations should be afforded any weight. *Novartis*, 853 F.3d at 1330 (for secondary considerations "to be accorded substantial weight, . . . a nexus must exist between the evidence and the merits of the

claimed invention" (citation and internal marks omitted)).

7. Blocking Patents Refute Long-Felt Need and Commercial Success

The potential deterrent effect of blocking patents is relevant "to understanding why others had not made, developed, or marketed that 'blocked' invention and, hence, to evaluating objective indicia of the obviousness of the later patent." *Acorda*, 903 F.3d at 1337, 1342. Specifically, in the context of commercial success, "a court must be assured that the patentee's market domination is not attributable to monopoly power or other economic coercion, or to other factors unrelated to patent validity." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 18, 36, (1966).

Here, any commercial success of IS is due precisely to Janssen's monopoly power and not to the validity of the '906 Patent. When the '906 Patent was filed, Janssen already owned three prior art patents that it had listed in the Orange Book as covering IS. (FF 416). Each of these patents "blocked" competitors from commercializing any aqueous nanoparticle paliperidone palmitate formulation prior to 2018, and thus prevented anyone from arriving at or practicing any of the particular dosing regimens made obvious by the prior art. Evidence of commercial success therefore should carry almost no weight. *See Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (blocking patents undermined commercial success when they block the ideas presented in the allegedly invalidating prior art).

In any event, Janssen has alleged that only a single commercial embodiment—IS—is commercially successful. But that embodiment was indisputably blocked through 2018. Thus, any evidence of commercial success of IS, or a long-felt need satisfied by it, is not probative of nonobviousness but rather of Janssen's serial patenting. *See Acorda*, 903 F.3d at 1337–38, 1342 (finding blocking patents undermined evidence of long-felt need and commercial success). And while Janssen never affirmatively put in any evidence of long-felt need, Dr. Kahn explained why IS and the '906 Patent did not solve any purported need. (*E.g.*, FF 476–478).

There should be no dispute that the '556 Patent, which was enforceable from October 19, 1993 until October 15, 2013, (FF 423) claims, among other things, the paliperidone palmitate compound. (FF 424–26). Janssen represented in its Orange Book submission that the '556 Patent covers the IS drug ***substance*** and the ***drug product***. (FF 425). The '556 Patent also claims "a method of treating warm-blooded animals suffering from psychotic diseases" by administering an "effective amount of the compound[s] of Claim 1," (DTX-69 at cl. 3; FF 424), which Janssen represented to the FDA also covered IS. (FF 425). Finally, Janssen received nearly 4 years of Patent Term Extension on the '556 Patent, based on the representation that claims 1 and 2 cover the paliperidone palmitate compound and an antipsychotic composition comprising paliperidone palmitate, respectively, and that claim 3

claims a method of using paliperidone palmitate.[13] Walsh Decl. Ex. A. Having obtained nearly four years of additional patent term based on these representations, Janssen should not be permitted to "play[] 'fast and loose' with the courts by prevailing twice on opposing theories" here. *United States v. Hallahan*, 744 F.3d 497, 510 (7th Cir. 2014). "[A]bsent any good explanation, a party should not be allowed to gain an advantage by litigation on one theory, and then seek an inconsistent advantage by pursuing an incompatible theory." *In re Kane*, 628 F.3d 631, 638 (3d Cir. 2010).

The '556—a "classic type of blocking patent" (Hofmann Tr. 2753:20-21)—blocked commercialization of ***any*** paliperidone product (whether oral, injectable, nasal, oil-based or aqueous) until its expiration after the filing date of the '906 Patent. (FF 423, 427). The existence of the '556 Patent alone should diminish any evidence of commercial success. *See Hofmann-La Roche Inc. v. Apotex Inc.*, Civil Action No.

[13] The prosecution history of the '556 Patent is a matter of public record, available at <https://portal.uspto.gov/pair/PublicPair> by entering the patent number. *See also*, *Uniloc USA, Inc. v. ADP, LLC*, 772 F. App'x 890, 898 n.3 ("The prosecution history is part of the intrinsic record of the patent and is a 'matter[ ] of public record. . . . It is thus subject to judicial notice."); *Horizon Medicines LLC v. Dr. Reddy's Labs., Inc.*, Civil Action No. 15-3324 (SRC), 2019 WL 6907531, at *5 n.4 (D.N.J. Dec. 18, 2019) (taking judicial notice of documents found in patent prosecution history); *Eagle View Techs., Inc. v. Xactware Sols., Inc.*, 325 F.R.D. 90, 97 (D.N.J. 2018) (taking judicial notice of "information that comes directly from the U.S. Patent Office's Image File Wrappers (electronic prosecution histories)."

07–4417 (SRC)(MAS), 2012 WL 1637736, at *18 (D.N.J. May 7, 2012) (discounting commercial evidence success based on existence of compound patent).

Janssen also owned two patents covering generic paliperidone palmitate formulations. The '843 Patent was enforceable from June 20, 2000 to May 12, 2017, (FF 430), and claimed a formulation comprising any aqueous formulation of paliperidone palmitate. (FF 432, 435). The '544 Patent was enforceable from April 29, 2003 to November 10, 2018, (FF 438), and claimed generic aqueous nanoparticle formulations of paliperidone palmitate. (FF 440). Both formulation patents had claims directed to methods of treating schizophrenia by administering "a therapeutically effective amount" of the claimed compositions, (FF 433, 441), which Janssen represented to the FDA also cover IS. (FF 433–434, 441–442). Thus, no competitor could have commercialized an aqueous paliperidone palmitate product prior to October 2017, nor a nanoparticle formulation prior to November 2018. (FF 434, 442). These patents merely added to the patent fortress Janssen built around paliperidone palmitate. (FF 437, 443).[14]

[14] To the extent Janssen seeks to discredit Mr. Hofmann's economic opinion related to the existence of the blocking patents because Dr. Wermeling did not testify at trial about those patents, that argument must fail as a matter of law. "Under settled evidence law, an expert may express an opinion that is based on facts that the expert assumes, but does not know, to be true. It is then up to the party who calls the expert to introduce other evidence establishing the facts assumed by the expert." *Williams v. Illinois*, 567 U.S. 50, 57 (2012). Through the patents themselves, Dr. Sinko's testimony, and Janssen's representations to the FDA and PTO regarding these patents, Teva has proven Mr. Hofmann's assumptions.

Taken together, these three patents afforded Janssen a complete monopoly over the paliperidone palmitate market.[15] Where, as here, "'market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.'" *Galderma,* 737 F.3d at 740; *Acorda*, 903 F.3d at 1337 (where the existence of prior patents "depressed incentives for others to invent the [claimed] dosing scheme," the inference of nonobviousness from evidence of commercial success is weak); *see also see also Sanofi-Aventis Deutschland GMBH v. Mylan Pharm., Inc.*, 791 F. App'x 916, 930 (Fed. Cir. 2019) (finding "weak" evidence of commercial success in view of other Orange Book-listed patents). Accordingly, the Court should discount any evidence of commercial success or long-felt need.[16]

Thus, the only relevant question—whether the facts Mr. Hofmann assumed are true—must be answered in the affirmative and Mr. Hofmann's opinion should be credited.

[15] Ms. Mulhern's suggestion that Janssen's patents would not have blocked others from "coming into the market with an alternative molecule" is a red herring. (Mulhern Tr. 2625:15-19). Whether other companies developed other products, such as risperidone, is "the absolute wrong inquiry" for purposes of evaluating whether Janssen's patents blocked others from "conceiv[ing] of the dosing regimen contained in the '906 patent with respect to paliperidone palmitate." (Hofmann Tr. 2756:7–14; FF 420); *Sanofi*, 791 F. App'x at 925 (evidence that other products that might address a similar need were not blocked is misplaced).

[16] Janssen attempted to diminish the significance of its blocking patents at trial by pointing to Teva's 2009 patent application claiming a process for the purification of paliperidone palmitate. (FF 444–446). Teva's application, however, is irrelevant, as "[i]t is elementary that a patent grants only the right to exclude

While Ms. Mulhern presented a theory at trial that Teva and other competitors could have developed a paliperidone palmitate product under 35 U.S.C. § 271(e)(1)'s safe harbor provision, what Ms. Mulhern failed to acknowledge is that any such product could not be commercialized. (FF 446). The mere fact that a competitor can conduct research in "blocked" space under the safe harbor provision "does not eliminate infringement liability for the eventual reward-collecting activity of generally marketing the product." *Acorda*, 903 F.3d at 1340–41; (FF 446). Quite the contrary: blocking patents "diminish[] possible rewards from a non-owner's or non-licensee's investment activity aimed at an invention whose commercial exploitation would be infringing, therefore reducing incentives for innovations in the blocked space." *See Acorda*, 903 F.3d at 1339.

8. There is No Nexus Between the Commercial Success of Invega Sustenna and the Claimed Dosing Regimen

Blocking patents aside, "evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial

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others and confers no right on its holder to make, use, or sell." *Vaupel Textilmaschinen KG v. Meccanica Euro Italia S.P.A.*, 944 F.2d 870, 879 n.4, (Fed. Cir. 1991); *see Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1559 (Fed. Cir. 1996) (finding "[t]hat BTG patented its unique purification method is irrelevant" to infringement); 35 U.S.C. § 154(a)(1). Even if Teva's patent had been granted, Teva would still be precluded from practicing its patented method until after at least the '556 Patent expired. At most, Teva's applications suggest that blocking patents do not preclude competitors from filing patent applications.

success." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006). There is no evidence tying IS sales to the claimed invention here. Ms. Mulhern's contrary opinions are based on the assumption that every unit of IS sold is used in accordance with the '906 Patent claims. (FF 449–451). Not so. REDACTED

REDACTED

REDACTED Moreover, patients receiving a second loading dose on days 4, 5, 11, or 12 or patients with renal impairment receiving 100/75 mg-eq. loading doses, both according to the IS label, also do not practice the claims. (FF 411). In sum, the data Ms. Mulhern used to conclude that IS is commercially successful included sales not attributable to the claimed invention. (FF 447–48). Without any ability to account for those sales or otherwise assess their significance, the Court should not consider them relevant to the obviousness of the '906 Patent.

Janssen also failed to show "that the driving force behind the product sales was a direct result of the unique characteristics of the claimed inventions." *WesternGeco LLC v. ION Geophysical Corp.*, 889 F.3d 1308, 1330–31 (Fed. Cir. 2018). To the contrary, when IS launched, Janssen was the only company promoting a branded long-acting injectable antipsychotic: Risperdal Consta. (FF 453). And after the release of IS, Janssen stopped all of its marketing efforts for Risperdal Consta, driving customers to IS instead. (FF 455). Indeed, as Dr. Kohler admitted, it became practically impossible to acquire Risperdal Consta for patients, (Kohler Tr.

1918:8–12), which necessarily inflated IS's sales. (FF 455).

Moreover, Janssen's "sophisticated and commercial marketing strategies" contributed to and explain the marketplace performance of IS. (FF 460). Ms. Mulhern did not dispute this fact. (*Id*.). Not only did Janssen strategically drive demand from Risperdal Consta to IS, it also (1) leveraged its vast influence in the oral antipsychotic market by providing samples of its oral Invega ER, the gateway to IS, which resulted in "a tremendous uptick" in IS sales, (FF 462-66), (2) relied on an "entrenched sales force" of more than 500 personnel to encourage prescriptions of IS, (FF 468), (3) spent more than $1.1 billion on marketing and promotional expenditures and an undisclosed amount more in launch expenditures, (FF 470), and (4) "gave away $2.5 billion in discounts and rebates in order to motivate prescribing behavior and use" of IS, (FF 474). All of these extrinsic incentives that indisputably drive IS sales and which Ms. Mulhern ignores are unrelated to the claimed invention, and undermine any assertion of commercial success. *See Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985).

III. CLAIMS 10, 13, 20 AND 21 LACK WRITTEN DESCRIPTION

Claims 10, 13, 20 and 21 (depending from claim 8) broadly claim "a dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient" comprising administering two loading doses "of from about 75 mg-eq." (SF 9 at cl. 10, 13, 20, 21; FF 656). But the inventors never invented ***any*** dosing regimen

for patients with moderate to severe renal impairment, nor ***any*** dosing regimen using amounts higher than 100 mg-eq. (FF 660).

Section 112 "requires a patentee to provide a written description that allows a person of skill in the art to recognize that the patentee invented what is claimed." *Synthes USA, LLC v. Spinal Kinetics, Inc.*, 734 F.3d 1332, 1341 (Fed. Cir. 2013). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor ha[d] possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

The '906 Patent specification provides just two passages that discuss administering paliperidone palmitate to patients with renal impairment. The first discusses administering doses of "about" 100/75 or 75/75 mg-eq. as two loading doses to patients with renal impairment. (FF 658). The second clarifies that "[f]or patients with renal impairment it would be desirable to adjust the loading doses to account for the increased exposure levels" to paliperidone, and that for patients "with ***mild*** renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses." (*Id.*) (emphasis added). Unsurprisingly, the '906 Patent does not mention regimens for patients with moderate or severe renal impairment, (FF 659), because the inventors never invented such a regimen. (FF 660–61). In fact, such a dosing regimen is not present in the IS label to this day. (FF 661).

Courts have consistently held that claims broader than what the inventors

actually invented fail the written description requirement. For example, in *Pernix Ireland Pain DAC*, the court found that the claims lacked written description where the inventors discovered that a specific formulation "did not require a dose adjustment for patients with mild or moderate hepatic impairment," but then broadly claimed a generic formulation. 323 F. Supp. 3d at 619. Likewise in *Synthes*, the Court found that the specification's disclosure of "grooves," which were a "species of 'opening'" did not "constitute an adequate disclosure to claim all openings." 734 F.3d at 1342. Similarly, in *Eli Lilly & Co. v. Perrigo Co.*, the court found that a claim calling for 10–10,000% penetration enhancer failed to meet the written description requirement because the specification described a single example containing 67% penetration enhancer. 202 F. Supp. 3d 918, 994–96 (S.D. Ind. 2016), *aff'd*, 718 F. App'x 953 (Fed. Cir. 2017). The court stated that although there was "adequate written description support for some narrower part of the range," there was no disclosure discussing "an amount anywhere near the upper end of the disclosed range," and thus there was "insufficient written description support for the entire range disclosed." *Id.* at 997.

The same is true here. Janssen does not dispute that the inventors only created a dosing regimen up to 100 mg-eq. for patients with ***mild*** renal impairment. (FF 660). Nor does Janssen dispute that the literal words of the claim are essentially unbounded in terms of degree of renal impairment or maximum dose. (FF 656).

Indeed, even accepting Janssen's view that a POSA would know the maximum dose would be 150 mg-eq., there is no disclosure anywhere that such a dose is suitable for patients with renal impairment, and the '906 Patent, in fact, teaches the opposite. (FF 664). For these reasons, claims 10, 13, 20 and 21 (as depending from claim 8) lack written description requirement.

IV. CLAIMS 20 AND 21 ARE INDEFINITENESS FOR FAILING TO CHARACTERIZE THE CLAIMED D(50) RANGE

Claims 20 and 21 require an "average particle size (d50) of from about 1600 nm to about 900 nm." How that limits the claims is uncertain, as was explained by Dr. Block at trial (FF 627). In response, Dr. Sinko offered anecdotes about what his students do in his lab (Sinko Tr. 1553:6–16), but his own textbook, which is used to instruct a POSA, corroborated Dr. Block's opinion. (FF 648). But even if Dr. Sinko were right—that machines can consistently read out a d50 value—that is insufficient to render the claims definite. Rather, "[a] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus*, 572 U.S. at 901.

The evidence at trial showed that, because the paliperidone palmitate particles at issue are asymmetrical and cannot be described by a single dimension, their size is reported as the diameter of a hypothetical "equivalent sphere" sharing some characteristic with the particles. (FF 628–29). But there are many ways to create an

"equivalent sphere" and measure its diameter (e.g., d_{max}, d_{min}, d_w, d_v, d_{sed}, d_s, d_{sieve}), and how the d50 is measured necessarily affects the value being reported. (FF 630). There are also different ways to express the particle size distribution (e.g., number-based, where half of the particles are smaller than the d50 value and half are larger; volume-based, where half of the total volume of the particles is below the d50 value and half of the total volume is above that value),[17] and how the distribution is expressed would again necessarily affect the d50 value. (FF 632–33). Indeed, even the choice of instrument and the experimental conditions can affect the d50 measurement. (FF 636–38). It was well-understood in the literature that "[d]ifferent techniques often give different results for three-dimensional particles" and thus "different results for particle sizes or particle size distributions." (DTX-129.0004–.0005; FF 63). Indeed, both the FDA and USP recognize that "[t]he same sample analyzed on different instruments ***more often than not*** produces different results." (FF 640). Yet, the '906 Patent provides no guidance to POSA on how exactly to measure the d50, including which distribution or instrument to use, or the

[17] Dr. Sinko did not dispute this fact, but rather suggested that a POSA would assume that a volume-based distribution should be used based on industry norms. (Sinko Tr. 2187:2–7). But the patent specification expressly suggests the use of a number-based distribution: "As used herein, an effective average particle size (d50) of less than 2,000 nm means that ***at least 50% of the particles*** have a diameter less than 2,000 nm when measured by art-known conventional techniques[.]"(DTX-1/PTX-1 at 7:32-36; FF 635).

experimental conditions or sample preparation procedure. (FF 646). Rather, the patent only says that the average particle size can be measured by "art-known conventional techniques." (FF 637). But if multiple methods are available that would "lead[] to different results without guidance in the patent or the prosecution history as to which method should be used," the claim is indefinite. *Dow Chem. Co. v. Nova Chems. Corp. (Can.)*, 803 F.3d 620, 634 (Fed. Cir. 2015). This is true even if POSA could determine the most appropriate method. *Id.* at 635; *Sandoz*, 789 F.3d at 1341.

Data obtained by both Janssen and Teva confirm the indefiniteness of the claims. REDACTED

REDACTED

REDACTED That is not a hypothetical difference. Dr. Sinko testified that he is unsure about the boundaries of the d50 range in the claim. (Sinko Tr. 1797:2–14, 1795:16–18). Only one thing, therefore, is clear—a POSA could not determine the scope of the claims with a reasonable degree of certainty. *Nautilus,* 572 U.S. at 901, 910.

In *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, the Federal Circuit found

the claim term "average molecular weight" indefinite because it could refer to one of three measurements—M_p, M_w, or M_n—each of which "would typically yield a different result," and the specification provided no clarity on which method to use. 789 F.3d 1335, 1341, 1344–45 (Fed. Cir. 2015). Like *Teva*, the '906 Patent specification fails to inform which of the numerous "art-known conventional techniques" should be used to measure d50.

In fact, this Court has previously held that the term "mean particle size"—a nearly identical term to the one at issue here—was indefinite for the exact same reasons. *Otsuka Pharm. Co. v. Torrent Pharm. Ltd.*, 151 F. Supp. 3d 525, 546 (D.N.J. 2015), *aff'd sub nom. Otsuka Pharm. Co. v. Zydus Pharm. USA, Inc.*, 694 F. App'x 808 (Fed. Cir. 2017). In *Otsuka*, this Court rejected arguments that POSA would, "based upon industry literature, understand the reference to 'particle size analysis via laser diffraction methods' as an instruction to construe 'mean particle size' as 'volume mean particle size,'" or d_v50, as Dr. Sinko asserts. *Id*. at 546. And while in *Otsuka*, the patent "identifie[d] a laser diffraction particle size analyzer," and claimed that "'mean particle size [be] measured using a laser diffraction particle size analyzer,'" *id*. (brackets in original), here the specification identifies four different methods of measuring particle size as non-limiting examples of "art-known conventional techniques," (FF 637), and lacks any corresponding description in the claim. Absent any teachings as to which d50 value, distribution, method, machine,

and sample preparation protocol to use, a POSA could not determine, with reasonable certainty, whether a particular formulation falls within the scope of claims 20 and 21. Accordingly, claims 20 and 21 are invalid.

V. CLAIMS 10, 20, AND 21 ARE INDEFINITES FOR FAILING TO CHARACTERIZE A "AQUEOUS NANOPARTICLE SUSPENSION"

Claims 10, 20, and 21 are also invalid for failing to define the bounds of the term "aqueous nanoparticle suspension." As Dr. Block, testified, this term lacks a typical meaning in the art. (FF 649). Although the '906 Patent states that "[t]he aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would have an average particle size (d50) of from about 1600 nm to 400 nm," (FF 117) such a disclosure "doesn't define a nanoparticle suspension" with any definite bounds; "there could be smaller or larger particles than those described in the specification," (FF 650–51; CL 139).

In fact, in the same paragraph describing the preferred size of the nanoparticles, the '906 Patent states "[s]uitable aqueous depot formulations are described in U.S. Pat. No. 6,077,843 (incorporated herein by reference)." (FF 652). But an examination of the '843 Patent shows "[s]uitable aqueous depot formulations" with particle exceeding 15,000 nm in size (or 15 micrometers). (*Id.*). As such, "[b]ased on the disclosure . . . in the specification," including references incorporated into the '906 Patent as teaching suitable formulations (such as the '544 and '843 Patents), a POSA could not "determine with reasonable certainty whether

some formulations are nanoparticle suspensions within the meaning of Claims 10, 20, and 21. (FF 653–55); *cf. Vapor Point LLC v. Moorhead*, No. 4:11-CV-4639, 2013 WL 11275459, at *16 (S.D. Tex. Dec. 18, 2013) (finding the term "micro-sized particles" sufficiently definite when the specification expressly defined it and gave consistent examples). The only thing the '906 Patent makes clear is that the term "nanoparticle," as used therein, has no clear upper limit.

VI. JANSSEN'S RULE 52(C) MOTION SHOULD BE DENIED

For the reasons stated above and in Teva's Response, (D.I. 142, incorporated herein), Teva has shown by clear and convincing evidence that the asserted claims of the '906 Patent are invalid, and Janssen's Rule 52(c) motion, stated on the record at the conclusion of trial, should be denied.

VII. CONCLUSION

At trial, Teva showed that the Representative Claims are obvious in view of the prior art, and also that all but claim 2 are invalid for failing to meet the definiteness and written description requirements. For the reasons stated above, Teva respectfully submits that the Court should find the '906 Patent invalid.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC. and JANSSEN PHARMACEUTICA NV, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 2:18-00734 (CCC)(MF) [redacted] *Electronically Filed*

DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S
PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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TABLE OF ABBREVIATIONS

Abbreviation	Exhibit/ Docket Ref.	Full Description
	D.I. 91	Janssen Pharmaceuticals Inc. and Janssen Pharmaceutica, NV's Motion for Correction of Inventorship Pursuant to 35 U.S.C. § 256
	DTX-2/ PTX-2	File History of U.S. Patent No. 9,439,906
PTO	D.I. 133	Final Pretrial Order
'544 Patent	DTX-54/ PTX-55	U.S. Patent No. 6,555,544 to François et al.
'548 Regimen	DTX-55/ PTX-54	NCT00210548 Summary on ClinicalTrials.gov
'556 Patent	DTX-69	U.S. Patent No. 5,254,556 to Janssen et al.
'591 Application	DTX-108/ PTX-69	U.S. Patent Appl. Pub. No. 2007/0197591 to Boom et al.
'843 Patent	DTX-71	U.S. Patent No. 6,077,843 to François et al.
'906 Patent	DTX-1/ PTX-1	U.S. Patent No. 9,439,906 to Vermeulen et al.
'918 Provisional	PTX-76	U.S. Provisional Patent Application No. 61/014,918
'952 Patent	DTX-803	U.S. Patent No. 5,158,952 to Janssen et al.
150/25		An injection of 150 mg-eq. paliperidone on Day 1, and 25 mg-eq. on Day 8
150/100		An injection of 150 mg-eq. paliperidone on Day 1, and 100 mg-eq. on Day 8
150/150		Injections of 150 mg-eq. paliperidone on each of Days 1 and 8
150/100/100/100		An injection of 150 mg-eq. paliperidone on Day 1, and 100 mg-eq. on Days 8, 36, and 64
150/150/100/100		Injections of 150 mg-eq. paliperidone on each of Days 1 and 8, and 100 mg-eq. on Days 36 and 64

Abbreviation	Exhibit/ Docket Ref.	Full Description
100/100		Injections of 100 mg-eq. paliperidone on each of Days 1 and 8
100/100/100/100		Injections of 100 mg-eq. paliperidone on Days 1, 8, 36, and 64
75/75/50/50		Injections of 75 mg-eq. paliperidone on each of Days 1 and 8, and 50 mg-eq. paliperidone on Days 36 and 64
2007 Haldol Label	DTX-149/ PTX-592	HALDOL® Decanoate (Haloperidol) Intramuscular Injection Label, Revised 2007
ANDA		Abbreviated New Drug Application
Asserted Claims		Claims 2, 10, and 13, and claims 20 and 21 of U.S. Patent No. 9,439,906
BMI		Body Mass Index
C.C.P.A.		United States Court of Customs and Patent Appeals
CL		Defendant Teva Pharmaceuticals USA, Inc.'s Proposed Conclusions of Law
Cleton 2007	DTX-84/ PTX-56	"PII-46 Effects of Renal Impairment on the Pharmacokinetic Profile of Paliperidone Extended-Release Tablets," from Volume 81, Supplement 1 of Clinical Pharmacology & Therapeutics in March 2007.
Cleton 2008	DTX 18/ PTX-53; DTX-19; DTX-20	Collection of: 1. Abstracts PI-74 and PI-75 from Volume 83, Supplement 1 of Clinical Pharmacology & Therapeutics, March 2008. 2. Two posters associated with PI-74 and PI-75, respectively, presented at the American Society for Clinical Pharmacology & Therapeutics ("ASCPT") in Orlando, Florida from April 2–5, 2008

Abbreviation	Exhibit/ Docket Ref.	Full Description
CQA		Critical Quality Attributes
Dep.		Deposition
Einarson	PTX-134	T.R. Einarson, et al., *Economic and Clinical Comparison of Atypical Depot Antipsychotic Drugs for Treatment of Chronic Schizophrenia in the Czech Republic*, J. Med. Econ., 16(9):1089-93 (2013)
Emsley	PTX-133	R. Emsley, et al., *Efficacy and Safety Profile of Paliperidone Palmitate Injections in the Management of Patients with Schizophrenia: An Evidence-Based Review*, Neuropsychiatric Disease & Treatment (14):205-223 (2018) "
EP'081	DTX-799	European Patent No. 0,904,081
EP'987	DTX-800	European Patent No. 1,033,987
Ereshefsky 1990	DTX-88/ PTX-59	L. Ereshefsky et al., *Kinetics and Clinical Evaluation of Haloperidol Decanoate Loading Dose Regimen*, Psychopharmacol. Bull. 26(1):108-114 (1990)
Ereshefsky 1993	DTX-89/ PTX-60	L. Ereshefsky et al., *A Loading-Dose Strategy for Converting from Oral to Depot Haloperidol*, Hosp. & Cmty. Psychiat. 44(12):1155-1161 (1993)
FDA		U.S. Food and Drug Administration
FF		Defendant Teva Pharmaceuticals USA, Inc.'s Proposed Findings of Fact
FRE		Federal Rule of Evidence
Gibaldi	DTX-91	S. Bhalla, *Parenteral Drug Delivery*, in Gibaldi's Drug Delivery Systems in Pharmaceutical Care (A. Desai & M. Lee, eds. 2007)
Goodman	DTX-93	Goodman & Gilman's the Pharmacological Basis of Therapeutics (L. L. Brunton et al., 11th ed. 2006) and/or (10th ed. 2001).

Abbreviation	Exhibit/ Docket Ref.	Full Description
IM		Intramuscular injection
Invega ER Label	DTX-102/ PTX-57	Invega™ (paliperidone) Extended-Release Tablets Label for NDA 21999, Revised 2006
Invega IR		Janssen's immediate release paliperidone injectable drug product
IS		Invega Sustenna
IS Label		Invega Sustenna© Label
Janicak	DTX-58/ PTX-67	P.G. Janicak & E. A. Winans, *Paliperidone ER: A Review of the Clinical Trial Data*, Neuropsychiat. Disease & Treatment 3(6):869-883 (2007)
Janssen		Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV
Janssen's Rule 52(c) Motion	D.I. 139	Plaintiffs' Motion for Judgment on Partial Findings Under Rule 52(c) Dismissing Defendant's Counterclaims and Defenses on patent Invalidity
Karagianis	DTX-96/ PTX-63	J. L. Karagianis et al., *Rapid Tranquilization with Olanzapine in Acute Psychosis: A Case Series*, J. Clin. Psychiat. 62(suppl. 2):12-16 (2001)
"Lawrence" or "Lawrence & Taylor supplements"	PTX-506	Lawrence et al., *Paliperidone palmitate: a new long-acting injection for schizophrenia*, Therapeutic Advances
NIH		National Institutes of Health
OB		Approved Drug Products with Therapeutic Equivalence Evaluations
Orange Book		Approved Drug Products with Therapeutic Equivalence Evaluations
PANSS		Positive and Negative Syndrome Scale
PK		Pharmacokinetic
POSA		Person of Ordinary Skill in the Art

Abbreviation	Exhibit/ Docket Ref.	Full Description
QALYs		quality-adjusted life years
Representative Claims		Claims 2, 10, and 13, and claims 20 and 21 of U.S. Patent No. 9,439,906
SF	D.I. 133 at 4-16	The parties' Stipulation of Facts set forth in the Final Pretrial Order
Teva		Teva Pharmaceuticals USA, Inc.
Teva's 2009 patent application	PTX-813	U.S. Patent Appl. Pub. No. 2009/0209757 to Ini et al.
Teva's ANDA		Teva's Abbreviated New Drug Application No. 211149
Tr.		Transcript
USP		United States Pharmacopeia
"USPTO " or "PTO"		United States Patent and Trademark Office
Verm.		Vermeulen
Walsh Decl.		December 11, 2020 Declaration of Liza M. Walsh In Further Support of Defendant Teva Pharmaceuticals USA, Inc.'s Trial Brief and Findings of Fact and Conclusions of Law
Werm.		Wermeling
WO'384	DTX-72/ PTX-66	International Patent Application Publication No. WO 2006/114384

Defendant Teva Pharmaceuticals USA, Inc. ("Teva" or "Defendant") respectfully submits its proposed Findings of Fact and Conclusions of Law.[1]

FINDINGS OF FACT

I. INTRODUCTION

3. This is a patent infringement action brought under the provisions of the Hatch-Waxman Act, 21 U.S.C. § 355, and the Patent Act, 35 U.S.C. § 271. (D.I. 133 at 2).

4. The procedural posture of this matter is set forth in the Joint Pretrial Order (D.I. 133 at 2, *see* SF 7, 8, 11, 12, 13, 16).

5. No party has contested that subject matter jurisdiction is vested in this Court pursuant to 28 U.S.C. §§ 1331 and 1338. (D.I. 133 at 2).

6. No party has contested personal jurisdiction or venue. (D.I. 133 at 2).

II. WITNESSES

A. Defendant

7. At trial, testimony from the following witnesses associated with Defendant were presented on the following topics.

1. Deposition Testimony By Plaintiffs' Designation

8. **Shawn Berg** is an employee of Teva Pharmaceuticals as the Director of

[1] Teva makes this submission based on its understanding of the arguments and positions Plaintiffs Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively, "Janssen" or "Plaintiffs") raised at trial. To the extent it is determined that any of Teva's Findings of Fact is more appropriately considered a Conclusion of Law, or vice versa, Teva incorporates it by reference.

Clinical Research. (Berg Dep. Tr. 6:18–19, 7:25–8:4).

9. **Muni Nerella** is an employee of Teva USA as the director of U.S. Portfolio, Generics. (Nerella Dep. Tr. 8:6–12).

10. **Andrea Rozman** is the leader of the Physical Characteristics Group of PLIVA, a subsidiary of Teva. (Rozman Dep. Tr. 17:5–12, 22:14–25).

2. René Kahn, Ph.D.

11. Dr. Kahn testified as an expert "in the fields of psychiatry, psychotic disorders, and schizophrenia." (Kahn Tr. 81:15–17).

12. Dr. Kahn is a psychiatrist trained in neurology, and is the chair of psychiatry at the Icahn School of Medicine in New York. (Kahn Tr. 73:23–74:1). He has extensive educational and work experience in the field. (*Id*. 74:13–75:10).

13. Dr. Kahn also has extensive experience with schizophrenia. He has treated patients and prescribed schizophrenia medications "[s]ince [his] residencies in the 1980s," (Kahn Tr. 75:11–17). He sees patients in private practice, and oversees the treatment of hundreds of patients in his role as a medical supervisor, (*id*. at 156:19-157:9), and chief of the research unit at the Bronx Veterans Affairs office, where he currently works, (*id*. at 74:24–75:10). He has also served as the president of the Schizophrenia International Research Society. (*Id*. 77:8–15).

14. Dr. Kahn has written "just over 1,000 peer-reviewed publications and [a] considerable number of them are about schizophrenia," including specific papers

about the treatment of schizophrenia. (Kahn Tr. 76:14–77:7).

15. Dr. Kahn recently completed a trial comparing aripiprazole and paliperidone palmitate with their long-acting equivalents. (Kahn Tr. 80:7–15, 2329:21–2330:23).

3. Daniel Wermeling, Pharm.D

16. Dr. Wermeling testified as an expert in pharmacy, clinical pharmacology, and drug development. (Werm. Tr. 199:4–6).

17. Dr. Wermeling is "a pharmacist by training and received a doctor of pharmacy degree in 1983." He then completed a two-year general clinical residence and a two-year drug development fellowship at the College of Pharmacy at the University of Kentucky. (Werm. Tr. 194:11–20).

18. Dr. Wermeling had "been a professor for 30 years at the University of Kentucky before [his] retirement in March of 2018," and has since been awarded the title of "emeritus professor." (Werm. Tr. 194:21–195:8).

19. Dr. Wermeling is a "serial entrepreneur." His current company is AntiOp Inc., but he also supports other startup companies, such as NX, where he is "the pharmacist in charge" of a product to treat brain tumors. (Werm. Tr. 194:21–195:8).

20. Dr. Wermeling has filed an "investigational new drug application and new drug applications with the FDA," and performed over 100 clinical studies throughout his career. (Werm. Tr. 195:15–196:22). Dr. Wermeling has experience formulating nasal forms of lorazepam, haloperidol, and naloxone. (*Id*. 197:4–14).

21. Dr. Wermeling received the "Institute Award" from the "American College of Clinical Pharmacy," and "was also awarded fellowship status for [his] contributions to the organization and to the profession." (Werm. Tr. 198:4–199:3).

22. Dr. Wermeling is the named inventor of U.S. Patent 8,198,291 directed to intranasal delivery of opioids. (Werm. Tr. 543:24–544:4, 544:20–25).

4. Lawrence Block, Ph.D.

23. Dr. Block testified as an expert in pharmaceutics. (Block Tr. 579:15–16).

24. Dr. Block obtained his "bachelor of science[] in pharmacy in 1962, and subsequently earned a master of science degree in pharmacy with a minor in chemistry [in] 1966. [In] 1969, [he] earned a Ph.D. in pharmacy with minors in chemistry and pharmacology and physiology." (Block Tr. 575:17–23).

25. Dr. Block was a professor at Duquesne University School of Pharmacy before becoming "chairman of the department of medicinal chemistry and pharmaceutics" as well as the "Director of the Center for Biotechnology". He retired in 2012, but remains a professor emeritus. (Block Tr. 575:25–576:14).

26. Dr. Block wrote "[s]everal chapters" of Remington's Science and Practice of Pharmacy, as well as the Comprehensive Pharmacy Review, and has published numerous peer-reviewed publications. (Block Tr. 576:17–577:6).

27. Dr. Block is also a recognized member of several professional organizations, and is "a member of the council of experts" on the United States Pharmacopeia

("USP") that "sets standards and specifications for drugs and the ingredients that go into those drugs" which are "enforced by the Food and Drug Administration by federal law." (Block Tr. 577:13–578:2, 578:10–17).

5. Ivan Hofmann

28. Mr. Hofmann testified as an expert in pharmaceutical economics. (Hofmann Tr. 2738:3–8). He has "been accepted as an expert in pharmaceutical economics in both federal and state courts," including in this District. (*Id*. 2737:19–2738:1).

29. Mr. Hofmann is "a vice president and managing director at Gleason IP, which is an economic accounting and financial consulting firm," (Hofmann Tr. 2735:21–25), and leads "intellectual property practice." (*Id*. 2735:25–2736:1).

30. Mr. Hofmann has "been retained by the USPTO and the Office of the Solicitor to testify on behalf of the U.S. Government," specifically "related to the issue of commercial success." (Hofmann Tr. 2737:12–16).

B. Plaintiff

31. At trial, testimony from the following witnesses associated with Plaintiffs was presented on the following topics.

1. Deposition Testimony By Defendant's Designation

32. **Frederick Tewell** is the "national sales director" at Janssen. (Tewell Dep. Tr. at 13:2–12; 34:21–34:24).

33. **Hal Woodrow** is a patent attorney employed by Janssen, and was responsible for the paliperidone palmitate project. (Woodrow Dep. Tr. at 9:4–10:11).

2. Dr. An Vermeulen

34. Dr. Vermeulen testified as a fact witness for Janssen. (D.I. 133 at 31).

35. Dr. Vermeulen is employed by Janssen Pharmaceutica in Beerse, Belgium, (Verm. Tr. 742:24–743:4).

3. Dr. Srihari Gopal

36. Dr. Gopal testified as a fact witness for Janssen. (D.I. 133 at 29–30).

37. Dr. Gopal is a senior director and development team leader at Janssen, and has extensive experience in the medical field. (Gopal Tr. 1038:25–1041:3).

38. Dr. Gopal did not join Janssen until April 2006. (Gopal Tr. 1040:6–11).

4. Dr. Mahesh Samtani

39. Dr. Samtani testified as a fact witness for Janssen. (D.I. 133 at 30-31).

40. Dr. Samtani is employed by Janssen as a scientist, (Samtani Tr. 1342:1–7), on pharmacometrics or pharmacokinetic modeling." (Samtani Tr. 1342:21–25).

41. Dr. Samtani is not a medical doctor, does not treat patients, and has no basis to know what happens outside of clinical trials. (Samtani Tr. 1446:11–18).

42. Prior to joining Janssen, Dr. Samtani had no work experience in the pharmaceutical field, and "had not created a population pharmacokinetic population model." (Samtani Tr. 1407:17-23, 1408:17–19).

43. Dr. Samtani first started working on paliperidone palmitate in February 2007 as a pharmacometric leader. (Samtani Tr. 1343:10–15). He joined the project to take over some of the duties of Dr. Vermeulen. (*Id*. 1343:17–22).

5. Patrick Sinko, Ph.D.

44. Dr. Sinko testified for Plaintiffs as an expert in drug formulation, drug delivery, pharmacy, and pharmacokinetics. (Sinko Tr. 1469:1–8).

45. Dr. Sinko is "a pharmacist and a pharmaceutical scientist" having little to no experience analyzing efficacy data. (Sinko Tr. 1462:24–1463:6;1698:12-1699:16).

46. Dr. Sinko is not a lawyer. (Sinko Tr. 1474:14–15).

47. Dr. Sinko "had a project" with Janssen before this litigation. (Sinko Tr. 1466:6–9).

6. Dr. Christian Kohler

48. Dr. Kohler testified for Plaintiffs as an expert on the treatment of psychotic disorders such as schizophrenia and in the management of the care of such patients with antipsychotics. (Kohler Tr. 1874:23–1875:1).

49. Dr. Kohler is "a psychiatrist at the University of Pennsylvania, where [he is a] professor of psychiatry and neurology." (Kohler Tr. 1869:13–18).

50. Dr. Kohler has "served as an investigator on several Janssen [clinical] trials." (Kohler Tr. 1873:24–1874:5).

7. Carla Mulhern

51. Ms. Mulhern testified for Plaintiffs "as an expert in the economic analysis of intellectual property." (Mulhern Tr. 2576:25–2577:1).

52. Ms. Mulhern is a "managing principal" at Analysis Group, Incorporated. (Mulhern Tr. 2574:17–18, 2575:16–17).

53. Ms. Mulhern is "not a medical [doctor]," (Mulhern Tr. 2667:23–24), nor is she a "technical expert in pharmaceutics." (*id*. 2667:25–2668:2).

III. BACKGROUND

A. Schizophrenia and Forms of Treatment

54. Schizophrenia is a chronic psychotic disorder that affects "[a]bout 1 percent of the population." (Kohler Tr. 1875:22–1876:7; Kahn Tr. 81:24–82:7; *see also* DTX-104/PTX-62 at 4; DTX-58/PTX-67 at 1).

55. Schizophrenia is generally treated with antipsychotic drugs. (Kahn Tr. 84:22–24; Kohler Tr. 1886:23–1887:10).

56. Chlorpromazine was the first antipsychotic drug, approved in the 1950's, (Kahn Tr. 92:3–8; Kohler Tr. 1891:16–1893:4; DTX-104/PTX-62 at 5), but numerous antipsychotic drugs have since been released in the U.S. and are still available today. (Kahn Tr. 92:9–14; Kohler Tr. 1891:16–1893:4).

57. Except for clozapine, introduced in 1960s, new antipsychotics have not "materially changed the outcome in schizophrenia". (Kahn Tr. 2296:11–2297:13).

58. "Oral medications are usually given . . . in the majority of cases in schizophrenia patients," and serve as "the first line treatment." (Kahn Tr. 90:1–5).

59. "Long-acting injectables are given when patients relapse, meaning when the symptoms return," (Kahn Tr. 90:6–10; *see also* Kohler Tr. 1887:14–1889:2, 1889:21–1890:7), or when patients "are not complaint or not adherent . . . with oral

medication," (Kahn Tr. 2303:8–2304:14; *see also* DTX-88/PTX-59 at 2 (p. 108)).

60. A long-acting injectable—often called a "depot" or "LAI"—can be made by linking the drug compound to another molecule, such as an ester, so that once the injectable is administered, it slowly releases into the bloodstream. (Kahn Tr. 85:17–86:4; Werm. Tr. 210:15–212:20; DTX-57.0003, Table I; DDX3-24).

61. As of 2007, LAIs were often prescribed "once a month and sometimes once every two weeks," which continues today. (Kahn Tr. 91:16–19; 2304:21–2305:4.

62. Regardless of the route of administration, once antipsychotic drugs are absorbed, they work in "exactly the same way" by "cross[ing] the blood brain barrier and block certain receptors" to cause a therapeutic effect. (Kahn Tr. 85:5–16).

63. Before initiating any LAI, a patient is given several doses of the oral version of the LAI. (Kahn Tr. 2395:14–2396:14). This is intended to determine whether a patient develops side effects such as dystonia and EPS, rather than an allergic reaction the latter being "extremely rare." (*Id.*).

B. Therapeutic Window

64. "One goal of therapeutics is to have a blood level [of a drug] rise to a level that's associated with therapy, with efficacy," but not exceed a level "associated with increasing side effects." (Werm. Tr. 285:9–286:5). This is known as the therapeutic window. (*id.*; *see also* Sinko Tr. 1540:5–16; DTX-93.0045; DDX3-47).

65. However, blood plasma levels are not a perfect correlation to efficacy. (Werm.

Tr. 382:8–18).

66. The brain receptor most targeted to treat schizophrenia is the dopamine-2 receptor, (Kahn Tr. 85:5–12; Kohler Tr. 1891:16–1892:7); when "65 to 80%" of the dopamine receptors are occupied by an antipsychotic drug, that would correlate to efficacy in most patients. (Werm. Tr. 287:22–288:6; DTX-104.0007).

IV. JANSSEN'S DEVELOPMENT OF ANTIPSYCHOTICS

67. As of 2007, Janssen had five FDA-approved antipsychotics indicated for use to treat schizophrenia on the market. (Mulhern Tr. 2708:9–13, 2709:14–18; Kahn Tr. 95:3–7; DTX-408.0001–0002; DTX-102.0006, 0026).

68. Janssen's typical antipsychotic drug development process begins with an oral form of a drug molecule, followed by an LAI form. (*See* DTX-287.0032).

69. The first antipsychotic used to treat schizophrenia that Janssen commercialized was haloperidol or Haldol, which the FDA approved in April 1967. (Verm. Tr. 746:1–13; Mulhern Tr. 2708:9–13).

70. Haldol decanoate, Janssen's LAI version of haloperidol, "was approved in January of 1986." (Mulhern Tr. 2709:14–18; Kohler Tr. 1893:1).

71. In 1993, Janssen gained approval for an oral antipsychotic drug called Risperdal, which contains the active ingredient risperidone. (Kahn Tr. 95:3–7, 96:8–9; DTX-106.0001, 0048).

72. Risperdal is indicated to treat "schizophrenia". (DTX-106.0001).

73. Once administered, the liver converts some of the risperidone to "9-hydroxy-risperidone," otherwise known as paliperidone, and both compounds work to block receptors in the brain to treat symptoms of schizophrenia. (Kahn Tr. 96:12–97:1, 97:6–16; Werm. Tr. 209:14–24, DTX-106.0028, 0036).

74. Janssen then launched Risperdal Consta, an LAI version of risperidone to treat schizophrenia. (Kahn Tr. 97:17–19, 98:3–5; DTX-408.0001–0002).

75. Janssen also developed Invega Extended Release ("ER"), an oral form of paliperidone first approved in 2006 to treat schizophrenia. (Kahn Tr. 99:23–100:4, 100:3–5; DTX-102.0006, 0026).

76. Following Invega ER, Janssen developed Invega Sustenna ("IS") (paliperidone palmitate), an LAI pro-drug of paliperidone indicated to treat schizophrenia. (Kahn Tr. 102:24–103:2, 104:6–11; DTX-11.0001).

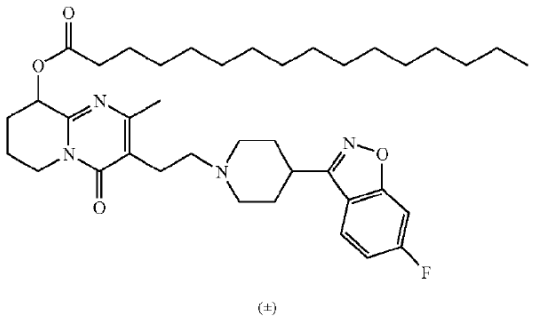
77. "Injectable formulations may be formulated in aqueous carriers." (DTX-1/PTX-1 at 7:19-20).

78. "Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, . . ., which are described in U.S. Pat. No. 5,254,556." ("the '556 Patent") (DTX-1/PTX-1 at 6:60-63).

79. Paliperidone palmitate, which is less water-soluble than paliperidone, remains in the muscle longer than an injection of paliperidone would. (Kahn Tr. 103:10–23; Werm. Tr. 211:16–212:20).

80. "The chemical name for paliperidone palmitate is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[l ,2-α]pyrimidin-9-yl hexadecanoate." (DTX-1/PTX-1 at 6:64-67).

81. The chemical structure of paliperidone palmitate is:



(±)

(DTX-1/PTX-1 at 7:1-14).

82. When paliperidone palmitate is administered, the body converts it to paliperidone, which slowly releases into the bloodstream. (Kahn Tr. 103:10–23; *see also* Werm. Tr. 283:16–284:15; Sinko Tr. 1520:18–25). In other words, after administration, "you won't be measuring paliperidone palmitate in the blood. You would simply be measuring paliperidone." (Werm. Tr. 287:5–13).

83. The '906 Patent admits that, prior to the invention, "[p]aliperidone esters may be formulated . . . into injectable dosage forms as described in [the '556 Patent] and U.S. Pat. No. 6,077,843" ("the '843 Patent"). (DTX-1/PTX-1 at 7:16-18).

84. "Prior to the '906 Patent it was "preferred to administer paliperidone palmitate in a once monthly aqueous depot. Suitable aqueous depot formulations are described in [the '843 Patent.]" (DTX-1/PTX-1 at 7:21-24; Sinko Tr. 1788:3-14).

V. INVEGA SUSTENNA

A. The Invega Sustenna Label

85. The Label uses the "full . . . molecular weight of the compound" paliperidone palmitate. (Gopal Tr. 1042:20–1043:9).

86. The following table represents doses of paliperidone palmitate and the equivalent doses of paliperidone:

INVEGA SUSTENNA (paliperidone palmitate)	
Prescribing Information Dosage Strength (milligrams of paliperidone palmitate)	Clinical Trial Dosage Strength (milligram equivalents of paliperidone)
39 mg	25 mg eq.
78 mg	50 mg eq.
117 mg	75 mg eq.
156 mg	100 mg eq.
234 mg	150 mg eq.

(DTX-19.0001; Gopal Tr. 1042:20–1043:9; DTX-11.0011, § 11; Werm. Tr. 283:16–284:15 (noting conversion factor of 0.6414)).

87. The Label recommends 150 mg-eq. on day 1 and 100 mg-eq. on day 8, both in the deltoid, and between 25–150 mg-eq. in the deltoid or gluteal monthly thereafter. (Kahn Tr. 104:14–22; Gopal Tr. 1042:10–19; DTX-11.0002, § 2.2).

88. The Label instructs that "[f]or patients naïve to oral paliperidone or oral or injectable risperidone, establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with Invega Sustenna." (DTX-11.0001).

89. Per the Label, the first two doses are reduced to 100/75 mg-eq., respectively, for patients with mild renal impairment; "Invega Sustenna is not recommended in patients with moderate or severe renal impairment." (DTX-11.0001, 0003).

B. The Formulation

90. Janssen ultimately settled on "F13" as "the final commercial formulation for Invega Sustenna." (Verm. Tr. 782:9–11; PTX-783 at 1; PTX-441 at 11).

91. REDACTED

REDACTED

C. The FDA Approval Process

93. Janssen filed with the FDA, "the NDA for Invega Sustenna® in October 2007." (Verm. Tr. 910:8–11; PTX-94 at 2 (JANUS00080447).

94. Janssen first sought approval only for a loading dose regimen of "100 [mg] on Day 1 in the deltoid, followed by another 100 [mg] on Day 8 in the deltoid." (Gopal Tr. 1096:3–24; *id*. at 1086:8–17; PTX-94 at 9 (JANUS00080454)).

95. At a pre-NDA meeting, Janssen obtained the FDA's "endorsement that they thought the [NDA] file was adequate." (Gopal Tr. 1166:15–21).

96. The FDA did not reject the proposed regimen as too high, it suggested "that [Janssen] go down as low as 75" mg-eq. for the first two loading doses, such that "physicians had the opportunity to choose," (Gopal Tr. 1102:10–21, 1210:11–25; PTX-94 at 9 (JANUS00080454)), but did not require the doses be the same on Days 1 and 8. (Gopal Tr. 1211:11–14).

97. Janssen presented predictions in "a table that shows the percentage of patients

that exceed" 7.5 ng/mL blood plasma concentration of paliperidone on certain days. (Gopal Tr. 1104:24–1105:9; PTX-348A at 6; PTX-370 at 63 (JANUS00558840)).

98. According to the predictions, "84 percent" of patients would reach the threshold for efficacy by Day 8 using a 150/100 mg-eq. loading dose regimen; "73 percent" for the 100/100 mg-eq. regimen; and "64 percent" for the 75/75 mg-eq. regimen. (Gopal Tr. at 1105:10–25; PTX-370 at 63).

99. Later, Janssen submitted a revised loading dose regimen that included a 150/100 mg-eq. loading dose regimen, which was approved in July 2009 without any pushback from the FDA. (Gopal Tr. 1106:15–19).

100. Janssen never conducted a clinical trial on the effect on renally-impaired patients, (Gopal Tr. 1213:25–1214:2); it relied on simulations limited "to patients with mild renal impairment," (Samtani Tr. 1440:25–1441:2).

VI. THE '906 PATENT

101. U.S. Patent 9,439,906 ("the '906 Patent") was filed on December 17, 2008, and issued on September 13, 2016. (DTX-1/PTX-1 at 1).

102. The '906 Patent claims priority to provisional applications: "61/014,918, filed on Dec. 19, 2007," and "61/120,276, filed on Dec. 5, 2008." (DTX-1/PTX-1 at 1).

103. The '906 Patent is only entitled to the priority date of December 5, 2008, provided by U.S. Provisional Application No. 61/120,276.

104. The '906 Patent names only two inventors: An Verm. and Alfons Wouters.

(DTX-1/PTX-1 at 1; Werm. Tr. 269:21–23).

A. The Prosecution History

105. During prosecution, Janssen submitted a copy of a prior art poster presented in Orlando, Florida, from October 11-14, 2007, which described the "Efficacy and Tolerability of Two Fixed Dosages of Paliperidone Palmitate in the Treatment of Schizophrenia: Results of a 9-Week Placebo-Controlled Study." (DTX-2/PTX-2 at 180–185, 236–42; Sinko Tr. 2061:17–18, 2062:9–20).

106. The poster described injecting 50 mg-eq. and 100 mg-eq. paliperidone palmitate on days 1, 8, and 36, and concluded PANSS total score improvement was "significantly different from placeby from Day 8" and that "[r]apid onset (by Day 8) of symptom improvement versus placebo was achieved for both the 50 and 100 mg eq. doses" and both were "well-tolerated." (DTX-2/PTX-2 at 238, 242)

107. The poster described injecting 50 mg-eq. and 100 mg-eq. paliperidone palmitate on days 1, 8, and 36, and concluded that "[r]apid onset (by Day 8) of symptom improvement versus placebo was achieved for both the 50 and 100 mg eq. doses" and both were "well-tolerated." (DTX-2/PTX-2 at 238, 242).

108. Application claim 1, filed on Dec. 17, 2008, (DTX-2/PTX-2 at 71), was directed to a regimen with injections of 100–150 mg-eq. in the deltoid on Day 1; 100–150 mg-eq. in the deltoid on "about" Days 6–10; and 25–150 mg-eq. in the deltoid or gluteal on "about the 34th to about the 38th day of treatment." (*Id*. at 54).

109. On December 12, 2011, Janssen amended claim 1 to recite loading doses of 150/100 mg-eq. on Days 1 and 8 "to more clearly describe what applicants' invention." (DTX-2/PTX-2 at 555, 560).

110. The Examiner's May 5, 2016 Reasons for Allowance stated that the claimed loading doses were non-obvious in view of only monthly dosing taught by "Francois et al. (US 6,555,544 B2)," and did not identify any prior art that disclosed loading doses (DTX-2/PTX-2 at 1654, 1659).

B. The Specification of the '906 Patent

111. The '906 Patent contains three Figures that purport to show a "population pharmacokinetic model simulation[]" and real data for the following regimens:

- Figure 1: 150/25/25/25 mg-eq. on Days 1, 8, 36 and 64;
- Figure 2: 150/100/100/100 mg-eq. on Days 1, 8, 36 and 64; and
- Figure 3: 150/150/150/150 mg-eq. on Days 1, 8, 36 and 64.

(DTX-1/PTX-1 at 4:46–60; Samtani Tr. 1414:1–5, 1414:16–19, 1415:5–8).

112. Figures 1–3 of the '906 Patent also appear in an internal Janssen slide deck. (Samtani Tr. 1415:19–23, 1417:16–1418:5; PTX-333 at 23 (slide 22)).

113. In the Figures, "the shaded region" is what the model originally predicted would occur, while the "clusters of dots" are "the actual data points that were observed" in Janssen's "[PSY-]3007" clinical study. (Samtani Tr. 1413:14–23, 1414:11–15, 1414:24–1415:4).

114. Dr. Samtani did not include all of the data points from the PSY-3007 study so

the data would fit the model better. (PTX-333 at 17; Samtani Tr. 1420:8-1421:14).

115. The ’906 Patent incorporates by reference the prior art ’556 Patent, which the ’906 Patent admits teaches that “[p]aliperidone esters,” including paliperidone palmitate, “are psychotic agents.” (DTX-1/PTX-1 at 6:60–64).

116. The ’906 Patent incorporates by reference the prior art ’843 Patent, which the ’906 Patent admits teaches “[s]uitable aqueous depot formulations” of paliperidone palmitate. (DTX-1/PTX-1 at 7:21–24).

117. The ’906 Patent incorporates by reference the prior art patent “U.S. Pat. No. 6,555,544,” which the ’906 Patent admits teaches “[s]uitable aqueous nano particle depot formulations” of paliperidone palmitate, (DTX-1/PTX-1 at 7:42–44), to be administered “once monthly,” (*id.* at 1:58-63; Sinko Tr. 1793:22–1794:1).

118. The ’906 Patent incorporates by reference prior art “WO2006/114384,” which the ’906 Patent admits teaches “[a]ppropriate methods to aseptically prepare paliperidone palmitate[.]” (DTX-1/PTX-1 at 11:33–36; Werm. Tr. 272:16–273:1; *see also* Sinko Tr. 1798:21–23).

119. The ’906 specification does not describe particle sizes “from about 1600 [nm] to about 900 [nm],” (Sinko Tr. 2143:2–6), or suggest this range is critical, but rather particle sizes “from about 1600 nm to 400 nm.” (DTX-1/PTX-1 at 7:25-31).

120. The ’906 Patent’s Example 5 states “an optimal particle size range is contained within xx-yy microm (d_{50v}),” (DTX-1/PTX-1 at 20:32-35), which does not

actually describe an optimal particle size. (Sinko Tr. 2143:21-2144:5).

121. The '906 Patent's Example 7 describes three different "optimized loading dose regimens," only the first of which is claimed. (DTX-1/PTX-1 at 23:16–24).

122. The '906 Patent's Example 8 describes the PSY-3007 clinical study, (Gopal Tr. 1177:24–1178:4), and states "the 150/100 arm of the study did not have efficacy as early as Day 8," whereas the 150/25 and 150/150 mg-eq. arms did. (Sinko Tr. 1702:12–21; DTX-1/PTX-1 at 23:26–31:49).

C. The Claims

123. Each claim of the '906 Patent is directed to a dosing regimen with three elements: "the time, meaning the day [] when an injection is administered; the site, meaning the muscle to which the needle is placed; and, [ ] the amount" to administer. (Werm. Tr. 270:3–15; DTX-1/PTX-1 at cls. 2, 10, 13, 20, 21).

124. The '906 Patent claims recite a range of alternative days on which certain injections may be administered, but the patient is only receiving a single injection within that range of days. (Kahn Tr. 108:18–23; Kohler Tr. 1945:12–16). Each day within the range defines a separate, alternative regimen covered by the claims.

125. The first maintenance dose of each claimed dosing regimen may be administered on "Days 27 to 48." (Kahn Tr. at 108:7–17, 111:22–112:10).

126. The second maintenance dose of claim 2 may be administered on "Days 48 to 86." (Kahn Tr. at 108:7–17).

127. Claims 2 and 13 recite "paliperidone palmitate [] formulated into a sustained release formulation" (Werm. Tr. 270:22–271:13; DTX-1/PTX-1 at cls. 1, 2, 11, 13).

128. Claim 10 is "a little more specific," in that the formulation is "an aqueous nanoparticle suspension." (Werm. Tr. 271:5–13; DTX-1/PTX-1 at cl. 10).

129. Claims 20 and 21 depend from claim 19 and provide "a recipe . . . explaining the contents of what is in the formulation" which are "standard excipients that are used in creating such a formulation." (Werm. Tr. 270:22–271:13; 271:25–272:12; DTX-1/PTX-1 at cls. 19–21).

130. Claims 20 and 21 also specify a minimum average particle size of "about 900" nm, which "has to include something less than 900." (Sinko Tr. 1795:19–21).

131. While not necessary, "the formulation that's in [claims] 19, 20 and 21, would [] also satisfy the more general descriptions in Claims 1 and 10[.]" (Werm. Tr. 271:14–17; DTX-1/PTX-1 at cls. 1, 2, 8, 10, 11, 13, 19–21).

VII. THE '918 PROVISIONAL APPLICATION

132. U.S. Provisional Application No. 61/014,918 ("the '918 Provisional") was filed on December 19, 2007. (PTX-76 at 1 (TEVAPALI0027260)).

133. The '918 Provisional names two inventors: An Vermeulen and Alfons Wouters, (PTX-76 at 5 (TEVAPALI0027264)), but neither signed an oath.

134. The '918 Provisional specification does not provide written description or even an embodiment of the claims later-issued in the '906 Patent. (PTX-76 at 11:1–

6 (TEVAPALI-0027270)).

135. The ’918 Provisional claims are are directed to a different dosing regimen compared to the claims later-issued in the ‘906 Patent. (PTX-76 at 35 (TEVAPALI0027295)).

136. Janssen’s expert did not provide an opinion as to whether a POSA reading the ’918 Provisional would understand that the inventors possessed a dosing regimen recited in the claims later-issued in the ’906 Patent. (Sinko Tr. 1591:2–8).

137. The ’918 Provisional does not provide a written description or even an embodiment of a formulation with an average particle size “of from about 1600 nm to 900 nm” as recited the claims later-issued in the ‘906 Patent. (*See* PTX-76 at 13 (TEVAPALI0027272))

VIII. DEFINITION OF A POSA

138. A POSA is a person who “would have an advanced degree such as an M.D., Ph.D., PharmD, master’s degree, or other advanced degree in an area related to chemistry, pharmaceutics, medicine or biology,” with “several years of experience in the pertinent field and be capable of working in a team comprising others in the field or related fields.” (Block Tr. 580:11–19; *see also* Kahn Tr. 114:14–24 (same); Werm. Tr. 202:22–203:8 (same)).

139. Although Janssen offers a different definition of a POSA, Drs. Wermeling and Block have the same opinions regardless of which definition the Court adopts.

(Block Tr. 580:23–25; Werm. Tr. 203:24–204:2).

IX. THE SCOPE AND CONTENT OF THE PRIOR ART

A. U.S. Patent 6,555,544 ("the '544 Patent)

140. The '544 Patent issued on April 29, 2003, (DTX-54/PTX-55 at 1), and therefore constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

141. The '544 Patent is assigned to Plaintiff. (DTX-54/PTX-55 at 1).

142. None of the named inventors of the '544 Patent overlap with the named or purported inventors of the '906 Patent. (*See* DTX-54/PTX-55 at 1).

143. The title of the '544 Patent is "Aqueous Suspensions of Submicron 9-hydroxyrisperidone fatty acid esters." (DTX-54/PTX-55 at 1).

144. "Submicron" refers to particles that are "below the size of a micrometer," or "nanometer." (Werm. Tr. 275:10–16; Sinko Tr. 1524:4–12).

1. The Paliperidone Palmitate Compound

145. The '544 Patent teaches that risperidone is metabolized into paliperidone. (DTX-54/PTX-55 1:54–57; Werm. Tr. 208:1–209:4).

146. The '544 Patent teaches the paliperidone "palmitate ester was found to be the superior ester from a pharmacokinetic, as well as from a tolerance point of view." (DTX-54/PTX-55 at 3:60–64).

2. The Formulation

147. The '544 Patent teaches how to make a sustained-release formulation of paliperidone palmitate that "is therapeutically effective for at least three weeks or

more, in particular about 1 month." (DTX-54/PTX-55 at 2:38–43).

148. The '544 Patent teaches a sustained-release formulation comprising a "prodrug," *i.e*. paliperidone palmitate, (Werm. Tr. 289:13–17; *see also* Sinko Tr. 1521:5–10), "a wetting agent," "one or more buffering agents" to render the formulation between 7.0–8.5, "a suspending agent," "preservatives" and "water". (DTX-54/PTX-55 at 7:49–58).

149. The '544 Patent teaches "[s]uitable suspending agents" include "polyethylene glycols," (DTX-54/PTX-55 at 6:61–67), "[s]uitable wetting agents" include "polysorbate 20," (*id*. at 7:2–8), and "[s]uitable buffering agents" should "render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5," (*id*. at 7:9–12; Werm. Tr. 545:21–24; Sinko Tr. 1521:17–22), and include "disodium hydrogen phosphate (anhydrous) . . . and sodium dihydrogen phosphate monohydrate," (DTX-54/PTX-55 at 7:12–16).

150. For a preservative, the '544 Patent taught the use of "benzyl alcohol." (DTX-54/PTX-55 at 7:17–25; Werm. Tr. 304:14–15).

151. The list of possible ingredients for the formulation described in the '544 Patent are all "very old excipients." (Werm. Tr. 289:18–290:5).

152. The '544 Patent teaches sterilizing the formulation with gamma irradiation, (DTX-54/PTX-55 at 8:48–51; Werm. Tr. 302:13–303:3).

3. The Particle Size

153. The ’544 Patent teaches a POSA to use nanoparticles of paliperidone palmitate, as “micronized” particles “have an exceptionally longlasting effect in humans.” (DTX-54/PTX-55 at 3:46–49; Sinko Tr. 1777:3–5).

154. The ’544 Patent teaches the particle size of a sustained release paliperidone formulation is a result effective variable that impacts “[t]he pharmacokinetic properties in humans[.]” (DTX-54/PTX-55 at 3:52–55).

155. The ’544 Patent teaches a preferred “effective average particle size of less than 2,000 nm,” which means “that at least 90% of the particles have a diameter of less than 2,000 nm[.]” (DTX-54/PTX-55 at 5:15–25).

156. The ’544 Patent teaches a POSA how to make nanoparticles of paliperidone palmitate, (Werm. Tr. 276:8–15; DTX-54/PTX-55 at 8:24–41), by starting with raw particles with a size “less than about 100 μm,” (DTX-54/PTX-55 at 5:20–25; 5:44–48), and “applying mechanical means,” such as a mill “to reduce the particle size of the antipsychotic agent to an effective average particle size of less than 2,000 nm,” (*id*. at 5:26–32, 6:1–3, 6:10–12; Werm. Tr. 294:20–25).

157. The ’544 Patent provides example nanoparticle suspension formulations, which differ only “by how long they are milled,” (Werm. Tr. 295:3–21); “Formulation A (micronized) was rolled for 0 hours, B for 4 hours, C for 7 hours and D for 38 hours.” (DTX-54/PTX-55 at 8:56–57; Werm. Tr. 295:3–21).

158. The ’544 Patent teaches the following particle size distributions of each

example formulation, obtained using a Mastersizer X:

	Particle size (μm)			
Formulation	10%	50%	90%	specific surface area (m^2/g)
A	2.51	6.03	7.64	1.3
B	0.62	1.38	6.83	6.5
C	0.52	0.74	1.15	13.5
D	0.43	0.52	0.65	>15

(DTX-54/PTX-55 at 9:19–32).

159. The '544 Patent teaches that nanoparticle formulations having a specific surface area >4 m^2/g are desirable. (DTX-54/PTX-55 at 3:65–4:3; Werm. Tr. 294:2–11; *see also* Sinko Tr. 1522:24–1523:21).

160. Example formulations "B, C and D" "have a surface area greater than 4" m^2/g. (Werm. Tr. 296:22–24; DTX-54/PTX-55 at 9:24–32); Sinko Tr. 1524:20–1525:3).

161. "Nothing" in the '544 Patent would "tell a person of ordinary skill in the art to not use Formulation B." (Werm. Tr. 546:6–9).

162. A POSA would consider formulations B, C and D for development. (FF 158).

163. The '544 Patent teaches a POSA sustained release paliperidone formulations that have particle sizes of about 1600 nm to about 900 nm. (FF 162–63).

164. Formulation B discloses a d_{50} of 1380 nm, (DTX-54/PTX-55 at 9:19–32), which is "of from about 900 nm to about 1600 nm."

165. Formulation C discloses a d_{50} of 740 nm, (DTX-54/PTX-55 at 9:19–32), which a POSA "would consider . . . about 900" nm. (Werm. Tr. 494:16–22).

166. A POSA would not be able to identify a material functional difference of a particle size distribution with a d_{50} of 740 nm and a d_{50} of 900 nm. (Werm. Tr. at 296:25–297:8; DTX-54/PTX-55 at 9:57–63) (showing similar experimental PK data in beagle dogs).

167. A POSA would "have been able to run a PK study in an animal like a beagle dog to measure the effect of particle size on PK of a formulation," as such experiments would be "[r]outine and necessary." (Werm. Tr. 298:5–11).

168. From the '544 Patent, a POSA would also "be able to create" formulations with particle sizes "that come somewhere between B and C" by changing the milling time. (Werm. Tr. 297:17–23).

4. The Injection Site

169. The '544 Patent teaches intramuscular injection in the deltoid or gluteus muscle, and possibly the upper thigh. (FF 168–170).

170. The '544 Patent teaches "administration via intramuscular or subcutaneous injection." (DTX-54/PTX-55 at 1:11–14; Werm. Tr. 277:20–278:2).

171. A POSA would have understood that "intramuscular" injections were "a very common injection technique." (Werm. Tr. 278:3–6).

172. A POSA "reading the '544 patent" would "understand that ['intramuscular'] would be the deltoid of your arm or the gluteus[.]" (Werm. Tr. at 280:16–21; *id*. at 556:6–11 (noting upper thigh another common area); Sinko Tr. 1719:15–17).

173. The '544 Patent taught that the paliperidone formulation should be "injected through a fine needle (*e.g.*, a 21 G 1 ½, 22 G 2 or 22 G 1 ¼)." (DTX-54/PTX-55 at 7:42–45). "21 or 22" refers to the needle diameter, and 1 ½, 2, and 1 ¼ refers to the needle length. (Werm. Tr. 280:24–281:14; Sinko Tr. 2090:13–25).

5. The Dosing Regimen and Amount

174. The '544 Patent teaches that sustained-release paliperidone palmitate formulations are useful to treat schizophrenia, and provides a method for doing so. (DTX-54/PTX-55 at 7:59–63, 8:9–11; Werm. Tr. 276:21–277:2).

175. The '544 Patent teaches "said formulation will be administered approximately every three weeks or even at longer intervals," (DTX-54/PTX-55 at 8:18–20), which a POSA would interpret as "[m]onthly." (Werm. Tr. at 281:25–282:2).

176. The '544 Patent teaches that, for monthly administration, "[t]he dosage should range from about 2 to 4 mg/kg body weight." (DTX-54/PTX-55 at 8:20–21; Werm. Tr. 282:20–25; Sinko Tr. 1531:7–17).

177. A POSA would assume most patients would weigh between 50–90 kg (or about 110–200 lbs), (Werm. Tr. 284:16–21), which corresponds to doses between 65–230 mg-eq. paliperidone palmitate, (*id*. at 284:16–21; *see also,* Sinko Tr. 2101:21–23, 2102:6–8 (agreeing with the math)), and includes a weight having a dose range of 75–150 mg-eq. (Sinko Tr. 2105:10–14).

178. A POSA would also know a dose of 115–135 mg-eq. would be suitable for

any patient between 50–90 kg. (*See* Werm. Tr. 284:16-21).

179. The '544 Patent teaches the therapeutic window for paliperidone is between 10–100 ng/mL paliperidone in the blood, (DTX-54/PTX-55 at 2:43–49; Werm. Tr. 286:15–25), and that staying within the therapeutic window is a "basic requirement[] that a contemporary depot formulation should fulfil in order to be acceptable for the intended patients." (DTX-54/PTX-55 at 2:60–64).

B. WO 2006/114384 A1 ("WO'384")

180. WO'384 is an "International [patent] Application Published Under the Patent Cooperation Treaty (PCT)" through the "World Intellectual Property Organization" (or WIPO). (DTX-72.0001/PTX-66).

181. WO'384 was published on November 2, 2006, (DTX-72/PTX-66 at 1), and therefore constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

182. The applicant of WO'384 is Plaintiff. (DTX-72.0001/PTX-66).

183. None of the named inventors of WO'384 overlap with the named or purported inventors of the '906 Patent. (*See* DTX-72/PTX-66 at 1).

184. WO'384 states that "3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-l-piperidinyl] ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one palmitate ester [] is also known as paliperidone palmitate ester." (DTX-72/PTX-66 at 1:15–17; *see also* Sinko Tr. 2147:1–7).

1. Background

185. WO'384 refers to "EP-0,904,081 and EP-1,033,987" for "aqueous suspensions of 'submicron' paliperidone palmitate (I) suitable as depot formulations which are therapeutically effective for about a month when administered intramuscularly." (DTX-72/PTX-66 at 2:1–4; Werm. Tr. 301:24–302:7).

186. EP-0,904,081 ("EP'081") claims priority to "PCT/EP97/02504," (DTX-799.0001), to which the '843 Patent also claims priority, (DTX-71.0001), meaning EP'081 and the '843 Patent are foreign equivalents of one another and share nearly word-for-word specifications. (*Compare* DTX-71 *with* DTX-799).

187. EP-1,033,987 ("EP'987") claims priority to "PCT/EP98/07321," (DTX-800.0001), to which the '544 Patent also claims priority, (DTX-54/PTX-55 at 1), meaning EP'987 and the '544 Patent are foreign equivalents of one another and share nearly word-for-word specifications. (*Compare* DTX-54/PTX-55 *with* DTX-800).

188. Dr. Sinko did not know that WO'384 referred to an equivalent of the '544 Patent when opining that there would be "no motivation to combine the teachings of the '544 patent with the teachings of the WO'384." (Sinko Tr. 2161:11–22).

189. A POSA would have been motivated to combine the '544 Patent with WO'384 because WO'384 identifies an improvement to the '544 Patent. (FF 197).

190. A POSA would know that "intramuscular[]" injections refers to "the deltoid, the buttocks and the vastus lateralis," or upper thigh. (Werm. Tr. 556:6–11).

191. WO'384 teaches injection of paliperidone palmitate in the deltoid, buttocks,

or upper thigh muscle. (FF 188).

2. The Formulation

192. WO'384 teaches a formulation comprising "a suspending agent, a buffer and an antioxidant," (DTX-72.0009/PTX-66 at 8:23–24), and that "[s]uitable buffering agents . . . should be used in an amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5." (*Id*. at 9:9–11; Werm. Tr. 303:22–304:7).

193. WO'384 teaches "[c]itric acid is useful as an antioxidant." (DTX-72.0010/PTX-66 at 9:15; Werm. Tr. 304:11–13).

194. A POSA would have known that citric acid was preferred over the benzyl alcohol used in the '544 Patent formulation because "the FDA now does not wish to see benzyl alcohol in pharmaceutical products." (Werm. Tr. 304:11–20).

195. Example 4 of WO'384 teaches the following formulation in Table 6:

Table 6

Name	Amount Required	
	Per ml	Quantity for 24 L
Paliperidone palmitate (sterile grade)	156 mg	3.744 kg
Polysorbate 20 parenteral	12 mg	288 g
Citric acid monohydrate parenteral	5 mg	120 g
Disodium hydrogen phosphate anhydrous parenteral	5 mg	120 g
Sodium dihydrogen phosphate monohydrate parenteral	2.5 mg	60 g
Sodium Hydroxide all use	2.84 mg	68 g
Polyethylene Glycol 4000 parenteral	30 mg	720 g
Water for injections q.s. ad	1000 µl	24 L

(DTX-72.0018/PTX-66 at 17).

196. WO'384 teaches a formulation with the same ingredients and concentrations

as that disclosed and claimed in the '906 Patent. (Werm. Tr. 305:4–6).

197. WO'384 teaches a formulation with the same ingredients and concentrations as that of Janssen's F13 formulation, the commercial formulation for IS. (Werm. Tr. 304:23–305:3; Sinko Tr. 2136:16–22; *see also* Verm. Tr. 782:9–11).

198. A POSA would know that injectable products must be sterile (or aseptic). (Werm. Tr. 302:13–303:3).

199. WO'384 teaches that "aseptic formulations of paliperidone palmitate (I) were initially obtained by gamma irradiation," referring to the method of the '544 Patent, but that was "found to give three breakdown products," (DTX-72.0003/PTX-66 at 2:4–6), which is "an undesirable outcome." (Werm. Tr. 302:13–303:3).

200. WO'384 teaches that "[i]n order to avoid the formation of the breakdown products . . . various other techniques to sterilize [paliperidone palmitate] were considered," (DTX-72.0003/PTX-66 at 2:19–20), and WO'384 provides "a new method of preparing the [paliperidone palmitate] product . . . through an aseptic production process" while maintaining the particle size. (Werm. Tr. 303:4–9; DTX-72.0004–0005/PTX-66 at 3:4–4:9; *see also* Sinko Tr. 1543:14–17).

201. WO'384 teaches an improved method of producing a sterile paliperidone palmitate formulation over the '544 Patent. (FF 197).

3. The Particle Size

202. The disclosure of the preferred particle size in WO'384 "parallels the previous

specification" found in the '544 Patent, (Werm. Tr. 303:13–19; Sinko Tr. 1544:10–23), in that the particles should have "a specific surface area >4 m^2/g," which means "that at least 90% of the particles have a diameter of less than 2,000 nm[.]" (DTX-72.0006/PTX-66 at 5:23–25, 7:25–26).

203. WO'384 teaches reducing the particle size using a "grinding process . . . as disclosed in EP-0,499,299." (DTX-72.0006/PTX-66 at 5:20–21; *see also id*. at 8:1–11; Werm. Tr. 303:13–19).

204. A POSA would know that the formulation taught in WO'384 could be milled to have particle sizes consistent with the four examples taught in the '544 Patent. (Werm. Tr. 326:14–327:2).

205. Examples 1–3 of WO'384 describe how to create "raw" paliperidone palmitate, which must be further processed before incorporation into a final formulation, and Tables 1-5 provide particle size measurements of raw paliperidone palmitate crystals *before* they are reduced in size for the final formulation. (Werm. Tr. 509:1–18, 510:8–15, 548:13–16, 550:9–15, 551:7–10; Sinko Tr. 1545:2–1546:4; DTX-72.0014–17/PTX-66 at 11–16).

206. A POSA would "understand that the crystals of the raw material [in Examples 1–3] were being further reduced through [a] milling process" in Example 4 to create a finished product. (Werm. Tr. 553:5–19, 554:5–9; DTX-72/PTX-66 at 17:22–18:3).

4. The Dosing Regimen and Amount

207. WO'384 teaches that, after making the final formulation, the target dose volume for the syringes was "between 0.25 ml and 1.50 ml depending on the dose needed," (DTX-72.0019/PTX-66 at 18:1–11, Table 7).

208. By multiplying the known concentration of paliperidone palmitate from Table 6 by the known target dose volume of Table 7, WO'384 teaches a dose amount ranging from 25 to 150 mg-eq. paliperidone, with the specific dose amount "depending on the dose that was needed . . . to treat a patient with schizophrenia." (Werm. Tr. 306:5–307:12; Sinko Tr. 2162:21–2163:1, 8–14).

5. Overlap With the '906 Patent

209. Tables 5, 6, and 7 of WO'384 are identical to Tables 1, 2, and 3 of the '906 Patent, respectively. (Werm. Tr. 552:14–23; *see* DTX-1/PTX-1; DTX-72/PTX-66).

210. "[T]he '906 Patent copied the manufacturing process for preparing nanoparticle size suspensions from the prior art WO'384 publication." (Werm. Tr. 555:5–8; Sinko Tr. 2136:16–19; *compare* DTX-1/PTX-1 at 14:27–16:58, *with* DTX-72/PTX-66 at 15:5–19:10).

C. NCT00210548 ("the '548 Regimen")

211. NCT00210548 ("the '548 Regimen") was published on September 20, 2005 on the National Institute of Health website called "ClinicalTrials.gov," (DTX-55/PTX-54 at 1; Werm. Tr. 315:23–316:3; Sinko Tr. 1578:13–24), and therefore constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

212. A POSA would look to ClinicalTrials.gov for information, as it is a "common strategy" for those in the field. (Werm. Tr. 317:3–7; Sinko Tr. 2196:13–18).

213. The '548 Regimen was not before the Patent Examiner during the prosecution of the '906 Patent. (DTX-1/PTX-1 at 1–4).

214. The '548 Regimen teaches that the "organization" running the study is Janssen's parent company, "Johnson & Johnson." (DTX-55/PTX-54 at 2).

215. The '548 Regimen is a published protocol summary of Janssen's internal study number PSY-3003. (Gopal Tr. 1164:20–25)

216. The '548 Regimen's "Official title" is "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 Mg Eq., 100 Mg. Eq., and 150 Mg Eq.) of Paliperidone Palmitate in Subjects With Schizophrenia." (DTX-55/PTX-54 at 1).

217. The '548 Regimen is a "Phase III" clinical trial. (DTX-55/PTX-54 at 1).

218. A POSA would understand that a Phase III clinical trial means that "this would be the stage where you are using doses that are thought to be safe and effective and are going to be confirmed in the larger patient population." (Werm. Tr. 316:17–317:2; *see also* Verm. Tr. 758:6–25; Gopal Tr. 1124:11–20).

219. The '548 Regimen dosing regimen is "[f]our injections of paliperidone palmitate 50, 100, 150 [mg-eq.] administered in the gluteal muscle (buttocks) . . . on Days 1, 8, 36, and 64[.]" (DTX-55/PTX-54 at 1; Werm. Tr. 317:13–23).

220. A POSA would know that the '548 Regimen "teaches loading doses on Days 1 and 8, followed by monthly dosing." (Werm. Tr. 317:13–23).

221. A POSA would know the '548 Regimen was not intended to evaluate different injection sites, only "that the 3 fixed doses of paliperidone are each more efficacious than placebo in treating [ ] schizophrenia." (DTX-55/PTX-54 at 1).

D. Gibaldi's Drug Delivery Systems ("Gibaldi")

222. The edition of Gibaldi, a well-known reference book "in circulation since at least the 1980[s]," (Werm. Tr. 279:9–13), relied upon was published in 2007 by a different inventive entity, (DTX-91/PTX-64 at 2), and thus constitutes 35 U.S.C. § 102(b) or at least 35 U.S.C. § 102(a) prior art to the '906 Patent.

223. Chapter 8 of Gibaldi discusses "Parenteral Drug Delivery," or injections, (DTX-91/PTX-64 at 3 (p. 103)), and teaches that "[t]he IM [intramuscular] injection site is usually the deltoid muscle of the upper arm or the vastus lateralis muscle in the . . . upper thigh." (*Id*. at 4 (p. 104); Werm. Tr. 278:20–279:2).

224. Gibaldi also teaches that "[a] needle long enough to reach deep into the muscle must be used" when giving an intramuscular injection, (DTX-91/PTX-64 at 4 (p. 104); Sinko Tr. 2089:17–2090:3), and "the depth of skin and fat would need to be taken into consideration" when selecting a needle. (Werm. Tr. 278:20–279:2).

225. Gibaldi teaches, "[t]he rate of absorption and extent of availability of drugs depend on [ ] factors such as formulation characteristics and the physiology of the

injection site," and that "IM injections given into the deltoid muscle in the arm are absorbed faster than gluteal injections" likely due to "the increased blood flow in the deltoid muscle and lower blood flow in the gluteus maximus muscle, which has a high content of adipose tissue." (DTX-91/PTX-64 at 5 (p. 105)).

226. Gibaldi states "IM injections are available in immediate-release formulations as well as depot formulations for sustained release." (DTX-91/PTX-64 at 5 (p. 105)). A POSA reading this section of Gibaldi would understand that its teachings apply to both immediate and sustained release formulations.

227. A POSA would have known and been motivated by the teachings of Gibaldi, including its teaching that injection of sustained release formulations into the deltoid muscle can allow for faster absorption than injection into the gluteal muscle.

E. Goodman & Gilman ("Goodman")

228. Although the parties presented two editions of Goodman (2001 and 2006), a well-known reference book "in circulation since at least the "1980[s]," (Werm. Tr. 279:9–13), the teachings relied on are the same in both, (PTX-65; DTX-93) and thus constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

229. A POSA would have generally known and been motivated by the teachings of Goodman, including its teaching that injection into the deltoid muscle can allow for faster absorption than injection into the gluteal muscle. (FF 228–29).

230. Goodman teaches the major routes for injections are "intravenous, subcutaneous, and intramuscular," and that "[g]enerally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus." (DTX-93.0032/PTX-65 at 8 (p. 7); Werm. Tr. 279:3–8).

231. Goodman teaches that the slower absorption has "been attributed to the different distribution of subcutaneous fat . . . and because fat is relatively poorly perfused. Very obese or emaciated patients may exhibit unusual patterns of absorption following intramuscular [] injection[s]." (DTX-93.0032/PTX-65 at 8).

232. Dr. Sinko failed to identify any statement in Goodman to support his position that the discussion of deltoid injections is limited to "aqueous *solutions*". (Sinko Tr. 1534:22–1536:21).

233. Dr. Sinko opined that an injectable suspension's absorption rate depends not on the injection site, but the formulation. (Sinko Tr. 1567:12-1568:4).

F. Drugs of the Future ("Revill")

234. Revill is an article titled "Paliperidone," published in Volume 31, Number 7 of "Drugs of the Future" in July 2006, (DTX-104/PTX-62 at 1), and thus constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

235. Revill teaches the therapeutic window necessary to "achieve[ ] 65–80% D2 receptor occupancy," was "15–25 ng/ml of paliperidone [immediate release] and

10–17 ng/ml of paliperidone [extended release].” (DTX-104/PTX-62 at 7; Werm. Tr. 288:7–12; *see also* Sinko Tr. 1738:19–24).

G. Ereshefsky 1990 and 1993

236. Ereshefsky 1990 and 1993 contain general teachings about loading doses of long-acting antipsychotics that a POSA would find relevant when designing a dosing regimen for paliperidone palmitate. (Werm. Tr. 312:7–16; Sinko Tr. 1789:19–25).

237. Ereshefsky 1990 and 1993 teach the use of haloperidol decanoate in an oil-based formulation, but a POSA would know that both oil- and aqueous-based formulations are “long-acting injection formulations by design intended for about monthly injection.” (Werm. Tr. 515:6–18).

238. Dr. Sinko’s opinions regarding Ereshefsky 1990 and 1993 are contradictory and not credible.

239. Dr. Sinko admitted that if a POSA wanted more rapid efficacy, “you would use a loading dose,” as in “the Ereshefsky references.” (Sinko Tr. 1789:19–25).

240. Both articles name Larry Ereshefsky as the first author. (DTX-88/PTX-59 at 2 (p. 108); DTX-89/PTX-60 at 3 (p. 1155)).

1. Ereshefsky 1990

241. Ereshefsky 1990 is an article titled “Kinetics and Clinical Evaluation of Haloperidol Decanoate Loading Dose Regimen,” published in Volume 26, Number 1 of the Psychopharmacology Bulletin from the National Institute of Mental

Health in 1990, (DTX-88/PTX-59 at 1-2), and therefore constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

242. Ereshefsky 1990 teaches a loading dose regimen for "haloperidol decanoate (HLD) [] a long-acting depot formulation of the [] antipsychotic haloperidol (HL)." (DTX-88/PTX-59 at 2 (p. 108); Werm. Tr. 313:5–8; Sinko Tr. 1566:9–13).

243. Ereshefsky 1990 teaches "[r]apid stabilization on depot antipsychotic can reduce the length of stay for acute inpatients, as well as decrease the recidivism rate, and decrease the total cost of care," compared to "[c]onventional, nonloading-dose, dosing regimens" that prolong stabilization and require oral supplementation that increases the risk side effects. (DTX-88/PTX-59 at 2 (p. 108)).

244. Ereshefsky 1990 goes on to teach that "[e]xtended periods of low [haloperidol ("HL") plasma concentrations ("Cps")] are typically observed following the first 'standard' 100-mg monthly injection of [haloperidol decanoate ("HLD")]. This may translate to increased risk of relapse in the stabilized patient converted to HLD or lack of efficacy in the acutely psychotic patient." (DTX-88/PTX-59 at 2 (p. 108)).

245. Ereshefsky 1990 teaches three available methods of converting "from oral therapy to HLD": "(1) use a low monthly dose of HLD, which will initially be subtherapeutic," until steady-state is reached after 90 days; (2) "supplement modest HLD doses with oral HL"; or (3) "use a larger initial dose to 'load' the patient, so that therapeutic effects are achieved more rapidly, and then reduce the initial dosage

to prevent excessive drug accumulation". (DTX-88/PTX-59 at 3 (p. 109)).

246. Ereshefsky 1990 teaches loading doses that are "20 times the previously administered oral haloperidol dose" to achieve steady-state plasma levels more rapidly. (DTX-88/PTX-59 at 2–3 (p. 108–09); Werm. Tr. 312:7–16).

247. Ereshefsky 1990 teaches dividing loading doses into "100 mg to 150 mg every 3 to 7 days until the full dose amount was administered," and using "a lower dose [thereafter] to compensate for drug accumulation." (DTX-88/PTX-59 at 2 (p. 108)).

248. Ereshefsky 1990 teaches that loading doses "were not associated with increased extrapyramidal symptoms." (DTX-88/PTX-59 at 7 (p. 113)).

249. Ereshefsky 1990 would have motivated a POSA to use loading doses for sustained release formulations of antipsychotic drugs, while providing a reasonable expectation of success in doing so. (Sinko Tr. 1789:19–25; Werm. Tr. 312:7–16).

2. Ereshefsky 1993

250. Ereshefsky 1993 is an article titled "A Loading-Dose Strategy for Converting from Oral to Depot Haloperidol," published in Volume 44, Number 12 of the Hospital and Community Psychiatry, A Journal of the American Psychiatric Association in December 1993, (DTX-89/PTX-60 at 1), and thus constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

251. Ereshefsky's 1993 notes that when initiating an LAI, "plasma concentrations can drop significantly," which "can lead to increased risk of relapse." Using "a

loading-dose paradigm," however, "reduce[s] the risk of relapse," and "depot neuroleptics decreases rates of patient noncompliance and increases patients' likelihood of avoiding hospitalization." (DTX-89/PTX-60 at 3 (p. 1155)).

252. Ereshefsky 1993 teaches, "[t]o reduce the risk of relapse when converting patients from oral to depot haloperidol," "use an initial monthly loading dose 20 times the patient's previous maintenance oral dose." (DTX-89/PTX-60 at 4 (p. 1156); Sinko Tr. 1568:21–1569:5).

253. Ereshefsky 1993 teaches that a large loading dose "avoids the use of oral supplementation." (DTX-89/PTX-60 at 4 (p. 1156)).

254. Ereshefsky 1993 teaches that "safety considerations led us to administer the loading dose in two or more sequential injections . . . every three to seven days until the full amount is given. To avoid excessive accumulation of the drug and thus increased side effects, the depot dose is reduced during the second and third months." (DTX-89/PTX-60 at 4 (p. 1156); Werm. Tr. 312:24–313:4).

255. Ereshefsky 1993 teaches, "[i]n patients placed on the loading dose regimen, plasma concentrations of haloperidol never dropped below the threshold associated with therapeutic response." (DTX-89/PTX-60 at 6 (p. 1158)).

256. Ereshefsky 1993 provides a flowchart with different initiation regimens, identifying as a "preferred strategy" the use of "haloperidol decanoate loading dose" without "overlapping oral medication." (DTX-89/PTX-60 at 8 (p. 1160)).

257. Ereshefsky 1993 teaches "[t]he loading-dose strategy for converting patients on oral haloperidol to haloperidol decanoate can safely and effectively maintain the clinical status of chronically ill patients." (DTX-89/PTX-60 at 8 (p. 1160)).

258. Ereshefsky 1993 would have motivated a POSA to use loading doses for sustained release formulations of antipsychotic drugs, while providing a reasonable expectation of success in doing so. (Sinko Tr. 1789:19–25; Werm. Tr. 312:7–16).

H. Karagianis

259. Karagianis is an article titled "Rapid Tranquilization With Olanzapine in Acute Psychosis: A Case Series," published in Volume 62, Supplement 2 of the Journal of Clinical Psychiatry in 2001, (DTX-96/PTX-63 at 1 (p. 12)), and thus constitutes 35 U.S.C. § 102(b) prior art to the '906 Patent.

260. Karagianis teaches,

> [a]cute, high-dose loading strategies (rapid neuroleptization) with the first-generation antipsychotics administered orally or parenterally . . . have been a commonly used treatment paradigm for controlling acutely agitated psychotic patients. The rationale was to achieve high plasma levels of drug within a shorter time period, resulting in rapid symptom mitigation.

(DTX-96/PTX-63 at 1 (p. 12)).

261. "[R]apid neuroleptization," is an older loading dose strategy," (Werm. Tr. 314:18–22), involving the "rapid use of oral . . . [or] short-acting intramuscular injections," and not long-acting injectables. (Kahn Tr. 2383:18–2384:11).

262. Karagianis analyzed "the use of up to 20 mg of an oral loading dose of

olanzapine," a second-generation antipsychotic known to be "well tolerated in doses ranging from 5 to 20 mg." (DTX-96/PTX-63 at 1 (p. 12)).

263. Karagianis used an "oral-loading strategy," starting a patient on "higher doses" of olanzapine "to try and get the patient's symptoms under control more quickly." (Werm. Tr. 313:16–314:7).

264. Karagianis would have motivated a POSA to use loading doses for antipsychotic drugs, while providing a reasonable expectation of success in doing so. (*See* Werm. Tr. 313:16–314:7).

265. The label for Zyprexa Relprevv—the LAI version of olanzapine—was not available until January 2018 and would not have been known to a POSA in 2007 when creating a dosing regimen for paliperidone palmitate. (Werm. Tr. 526:9–15; Sinko Tr. 1476:16–1477:4; PTX-93 at 1 (JANUS01758888)).

I. Janicak

266. Janicak is an article titled "Paliperidone ER: a review of the clinical trial data," published as an "Expert Opinion" in Neuropsychiatric Disease and Treatment, Volume 3, Issue 6 in 2007 by a different inventive entity than the '906 Patent, (DTX-58/PTX-67 at 1 (p. 869); Sinko Tr. 1582:7–8), and thus constitutes at least 35 U.S.C. § 102(a) prior art to the '906 Patent.

267. Janicak was co-authored by Elizabeth Winans, an employee from Janssen. (DTX-58/PTX-67 at 1 (p. 869); Werm. Tr. 315:2–12).

268. Janicak teaches "paliperidone palmitate is currently in Phase III development as an aqueous, nanotechnology-based, long-acting injectable (LAI) formulation," (DTX-58/PTX-67 at 14 (p. 882)), and that "[t]he first two injections [of paliperidone palmitate] will be administered as a loading dose within 7 days of initiation." (*id.*; Werm. Tr. 315:2–12; Sinko Tr. 1581:20–1582:6).

269. Janicak would have motivated a POSA to use loading doses for sustained release paliperidone palmitate formulations on Days 1 and 8, while providing a reasonable expectation of success in doing so. (*See* Werm. Tr. 314:25–315:12).

J. '591 Application

270. The '591 Application was published on August 23, 2007 by a different inventive entity, (DTX-108/PTX-69 at 1), and thus constitutes 35 U.S.C. § 102(b) or at least 35 U.S.C. § 102(a) and/or § 102(e) prior art to the '906 Patent.

271. The '591 Application refers to Johnson & Johnson. (DTX-108/PTX-69 at 1).

272. The '591 Application reflects many of the teachings from the '544 Patent, including incorporating by reference the '556 and '843 Patents, (DTX-108/PTX-69 at ¶¶ 0013, 0018), teaching "paliperidone palmitate," (*id.* at ¶ 0015), and providing example aqueous formulations, (*id.* at ¶ 0016), as well as preferred particle sizes with a surface area greater than 4 m^2/g, (*id.* at ¶ 0017).

273. The '591 Application teaches that "[p]sychiatric patients often have comorbid conditions," and it would be desirable to avoid drug metabolization in the liver.

(DTX-108/PTX-69 at ¶ 0003).

274. Rather than the liver, the '591 Applicant teaches that paliperidone "is eliminated from the body via the kidney and is excreted in the urine." (Werm. Tr. 328:25–329:6; Sinko Tr. 1585:20–1586:10; DTX-108/PTX-69 at ¶ 00039).

K. Cleton 2007

275. Cleton 2007 is an Abstract from "Johnson & Johnson PRD" titled "PII-46[:] Effects of Renal Impairment on the Pharmacokinetic Profile of Paliperidone Extended-Release Tablets," published in Volume 81, Supplement 1 of Clinical Pharmacology & Therapeutics in March 2007, by a different inventive entity than the '906 Patent, (DTX-84/PTX-56 at 1), and thus constitutes 35 U.S.C. § 102(b) or at least 35 U.S.C. § 102(a) prior art to the '906 Patent.

276. Cleton 2007 teaches, "[p]aliperidone is primarily excreted renally in humans." (DTX-84/PTX-56 at 1).

277. Cleton 2007 teaches that "[s]ubjects with mild, moderate and severe renal impairment had mean C_{max} and AUC_{∞} values that were approximately 1.6, 2.5, and 2.1 times, respectively and approximately 1.5, 2.8 and 3.4 times higher compared with healthy subjects." (DTX-84/PTX-56 at 1). In other words, "the two measures of exposure . . . , the maximum concentration, designated as C_{max}, and the total exposure by AUC, as area under the curve, is basically doubling for patients who have renal impairment." (Werm. Tr. 330:24–331:5).

278. Cleton 2007 would provide "strong consideration" to a POSA "for reducing the dose" of paliperidone in renally impaired patients. (Werm. Tr. 331:6–9).

L. Invega ER Label

279. The Invega ER Label was published by December 19, 2006 by a different inventive entity than the '906 Patent, (DTX-102/PTX-57; Werm. Tr. 331:18–22); it thus constitutes 35 U.S.C. § 102(b) or at least § 102(a) prior art to the '906 Patent.

280. The Invega ER Label teaches "[t]he maximum recommended dose" of oral paliperidone "is 12 mg/day." (DTX-102/PTX-57 at 25).

281. The Invega ER Label also teaches that "[f]or patients with mild renal impairment . . . the maximum recommended dose is 6 mg once daily. For patients with moderate to severe renal impairment . . . , the maximum recommended dose [ ] is 3 mg once daily." (DTX-102/PTX-57 at 25).

282. A POSA would understand that, compared to patients with normal renal function, the Invega ER Label teaches that the maximum daily recommended dose of paliperidone "requires a 50 percent dose reduction from the maximum dose for patients with mild renal impairment." (Werm. Tr. 332:21–333:12).

283. The Invega ER Label taught a 50% reduction from the "recommended" dose of 6 mg to the "maximum recommended dose" of 3 mg for patients with moderate or severe renal impairment. (DTX-102/PTX-57 at 25; Werm. Tr. 332:1–9).

M. Cleton 2008

284. Because the '906 Patent invention date is its effective filing date of no earlier than December 5, 2008, the Cleton 2008 references constitute additional prior art to the '906 Patent under 35 U.S.C. § 102(a). (Werm. Tr. 337:11–17).

285. Cleton 2008, collectively, refers to two abstracts (PI-74 and PI-75) published in March 2008 and the associated posters presented from April 2–5, 2008. (Werm. Tr. 337:11–17; DTX-18/PTX-53; DTX-19.0001; DTX-20.0007).

286. A POSA "would look at both [PI-74 and PI-75 abstracts] at the same time" since "they were published next to each other on a piece of paper and . . . they deal with the same subject matter." (Werm. Tr. 341:10–16)

287. Cleton 2008 "is supplementary and confirmatory" of what a POSA already knew as of December 19, 2007. (Werm. Tr. 348:17–20).

1. PI-74 Abstract

288. The first abstract is titled "PI-74". (DTX-18/PTX-53 at 1).

289. "Johnson & Johnson" is associated with PI-74. (DTX-18/PTX-53 at 1).

290. PI-74 was a single-dose "[s]tudy [to] evaluate[] the dose proportionality of paliperidone palmitate injections administered in either gluteal or deltoid muscle." (DTX-18/PTX-53 at 1).

291. A POSA would understand that PI-74 sought to understand the dose proportionality of paliperidone palmitate (from 25–150 mg-eq.), and the impact of the injection site. (Werm. Tr. 338:3–14).

292. PI-74 teaches total exposure "increased proportionally with increasing paliperidone palmitate doses (25–150 mg-eq.) regardless of gluteal or deltoid injection," but also that deltoid injections generally led to higher plasma concentrations, earlier, than gluteal injections. (DTX-18/PTX-53 at 1).

293. A POSA would conclude that deltoid injections were more effective and faster, (Werm. Tr. 339:20–340:4), consistent with Gibaldi. (FF 223).

294. PI-74 is "confirmatory" of what a POSA would already know and expect. (Werm. Tr. 340:5–9).

2. PI-74 Poster

295. The poster associated with PI-74 contains additional information, data, and figures not found in the abstract. (*See generally* DTX-19).

296. In particular, the PI-74 poster teaches the paliperidone formulation used was "an aqueous nanosuspension . . . allowing for once-monthly dosing[.]" (DTX-19.0004; Werm. Tr. 344:22–345:12).

297. The PI-74 poster teaches that the formulation can be administered "without the need for oral supplementation." (DTX-19.0004; Werm. Tr. 346:2–7).

298. The PI-74 poster also confirms that the entire dose range of "[p]aliperidone palmitate (25–150 mg eq.) was well tolerated after a single injection into the deltoid or gluteal muscle." (DTX-19.0009).

3. PI-75 Abstract

299. The second abstract is titled "PI-75[:] Evaluation of the Pharmacokinetic Profile of Gluteal Versus Deltoid Intramuscular Injections of Paliperidone Palmitate 100 mg Equivalent In Patients With Schizophrenia." (DTX-18/PTX-53 at 1).

300. "Johnson & Johnson" is associated with PI-75. (DTX-18/PTX-53 at 1).

301. A POSA would understand that PI-75 "was comparing the gluteus and the deltoid muscles" by "administer[ing] 100 [mg-eq.] as a fixed dose." (Werm. Tr. 340:13–18; Sinko Tr. 1603:1–7; DTX-18/PTX-53 at 1).

302. A POSA would understand that the PI-75 dosing regimen involved "two initial . . . injections on Days 1 and 8 . . . and at monthly intervals thereafter." (Werm. Tr. 346:12–23; Sinko Tr. 1603:1–7; DTX-18/PTX-53 at 1).

303. PI-75 teaches a higher maximum concentration of paliperidone from deltoid injections than gluteal injections. (DTX-18/PTX-53 at 1).

304. PI-75 also tracked the pain experienced at the injection site, "and it shows [the deltoid injections were] well tolerated." (Werm. Tr. 398:4–20, 399:9–11; Werm. Tr. 340:19–25; DTX-18/PTX-53 at 1).

4. PI-75 Poster

305. The poster associated with PI-75 contains additional information, data, and figures not found in the abstract. (*See generally* DTX-20).

306. In particular, the PI-75 poster the paliperidone formulation used was "an aqueous nanosuspension . . . allowing for once-monthly dosing[.]" (DTX-20.0002).

307. The PI-75 poster teaches that the formulation can be administered "without the need for oral supplementation." (DTX-20.0002; Werm. Tr. 347:5–11).

308. The PI-75 poster teaches the differences between deltoid and gluteal injections "can likely be explained by the different distribution of muscle and adipose tissue between the two injection sites. The hypovascularity of subcutaneous adipose tissue compared with muscle tissue may result in slower uptake of paliperidone from the gluteal compared with the deltoid[.]" (DTX-20.0007).

309. The PI-75 poster also confirms that "[m]ultiple injections of paliperidone palmitate (100 mg eq.) were well tolerated[.]" (DTX-20.0007).

310. A POSA would read the PI-75 Poster as showing "the loading dose regimen [on] Days 1 and 8 had proven to resolve in faster attainment of steady state paliperidone plasma concentrations." (Werm. Tr. 346:12–23).

X. MODIFYING THE PRIOR ART

A. Presumption of Obviousness

311. The dose amounts and injection sites of paliperidone palmitate taught by the '544 Patent (e.g., 75–150 mg-eq.) encompass or overlap the dose amounts and injection sites claimed in the '906 Patent. (SF 9; FF 177).

312. The dose amount taught by WO'384 (25–150 mg-eq.) are identical and entirely overlap the dose amounts claimed in the '906 Patent, and the injection sites encompass those claimed in the '906 Patent. (SF 9; FF 208).

313. The dose amounts taught by the '548 Regimen (50, 100, 150 mg-eq.) overlap with the dose amounts claimed in the '906 Patent, and the days of administration (1, 8, 36, 64) fall within the ranges claimed in the '906 Patent. (SF 9; FF 219).

314. A POSA would have been motivated to experiment with, select, and optimize dose amounts taught by the '544 Patent, WO'384, and/or '548 Regimen.

315. Janssen did not offer any facts or evidence sufficient to overcome a presumption of obviousness.

B. Obviousness of the General Dosing Regimen

316. Dr. Wermeling did not use hindsight bias to arrive at his opinion on obviousness. (Werm. Tr. 199:23–200:8, 205:4–18, 348:6–16).

317. Dr. Wermeling does not think all drug development is obvious and unpatentable. (Werm. Tr. 544:18-545:7; FF 22).

318. Dr. Wermeling's opinions on obviousness are well-supported and credible.

1. Monthly Injections of Paliperidone Palmitate

319. A POSA would have known that paliperidone palmitate "had been developed to provide sustained release plasma concentrations of paliperidone when administered once monthly, which greatly enhances the compliance with dosing." (Sinko Tr. 2086:5–12; DTX-71 at 2:63-67; DTX-54/PTX-55 at 2:38-43).

320. A "one-month interval for a long-acting injection would be desirable for a lot of reasons," such as "compliance [and] scheduling." (Werm. Tr. 282:11–16).

321. A POSA was also "already taught you could treat schizophrenia with a therapeutically effective amount of paliperidone palmitate injected IM, intramuscular, once monthly with a nanoparticle suspension." (Sinko Tr. 1788:11–14; 1789:12–18; 2153:13–22).

322. Dr. Sinko was "not offering an opinion that a person of skill in the art could not practice [claim 7] of the '544 Patent] without undue experimentation." (Sinko Tr. 1764:21–1765:1, 14–20).

323. A POSA also would have known that with monthly injections, alone, "it takes four to five half-lives to get to steady state." (Werm. Tr. 385:7–16).

324. "[S]peeding onset of efficacy for an antipsychotic drug would be a known important goal. . . in 2007." (Sinko Tr. 1793:2–5; Gopal Tr. 1054:13–22).

325. A POSA would have been motivated to adapt the monthly dosing regimens taught by the '544 Patent and WO'384 to "accelerate the onset of effect" of monthly doses of paliperidone palmitate. (Werm. Tr. 311:18–23).

326. A POSA would have been further motivated to adapt the monthly dosing regimens taught by the '544 Patent and WO'384 to reduce the length of hospital stays for acute patients, decrease the recidivism rate, decrease the total cost of care, and decrease instances of relapse. (*See* FF 243, 252).

2. Selecting Dose Amounts and Times

327. Selecting dose amounts and dose times was not unpredictable to a POSA.

328. A POSA would expect that "the C_{max} from a single dose is related to the amount of the dose given." (Sinko Tr. 2118:24–2119:2).

329. A POSA would know that if a first dose fails to reach a therapeutic threshold in a given time, a higher dose could reach the threshold in the same amount of time. (Sinko Tr. 2112:8–15).

330. A POSA would therefore understand and reasonably expect that, relative to a lower dose (e.g., 100 mg-eq.), a higher dose (e.g., 150 mg-eq.) of paliperidone palmitate is more likely to reach the therapeutic threshold. (FF 327).

331. A POSA would know that the peak after a second dose depends on the amount of the second dose; "a lower second dose is likely to give a lower second peak than giving a higher second dose." (Sinko Tr. 2119:3–6, 2120:13–16).

332. A POSA would also expect that "if you give the second dose earlier in time, your second peak is going to be higher than if you give the second dose later in time," the dose amounts being equal. (Sinko Tr. 2120:23–2121:6).

333. A POSA would "understand that there is a target efficacy concentration for paliperidone in the blood of schizophrenic patients[.]" (Sinko Tr. 2123:18–23).

334. A POSA would know "what the target for the paliperidone plasma levels were to achieve safety and efficacy." (Sinko Tr. 2135:11–2124:3; FF 179).

3. Selecting Loading Doses

335. Ereshefsky 1990 and 1993, Karagianis, and/or Janicak would have provided

a POSA a motivation to adapt the monthly dosing regimens taught by the '544 Patent and WO'384, with a reasonable expectation of success in doing so.

336. A POSA would have known there are two options to speed up efficacy of long-acting antipsychotic drugs: (1) administer loading doses, or (2) supplement the first injections with an oral form of the drug. (FF 245; Werm. Tr. 345:13–346:1).

337. A POSA would have known that loading doses are an old, well-known, and routine technique to achieve therapeutic plasma levels rapidly. (Sinko Tr. 1789:19–25, 1792:16–1793:5; Verm. Tr. 969:23–25; FF 242, 252, 260).

338. A POSA would know that, because long-acting injectables are often used for patients who failed to adhere to oral tablets, loading doses would be a preferred strategy to oral supplementation. (*See, e.g.*, FF 59, 256).

339. "[O]nce knowing that paliperidone palmitate could be administered as a long-acting injectable once monthly," a POSA would "be motivated to try loading dose regimens" "if their goal was to speed onset." (Sinko Tr. 1792:16–1793:5; *see also id.* at 1789:19–25; Verm. Tr. 969:10–15 (agreeing loading doses are "a quite commonly applied principle.").

340. A POSA would have been motivated administer a monthly paliperidone palmitate formulation as loading doses to attain therapeutic plasma concentrations quickly, eliminate the need for oral supplementation, reduce the risk of relapse, and decrease the total cost of care. (FF 243, 252–253, 326; Werm. Tr. 312:7–16).

341. A POSA would have known that the formulation disclosed by either WO'384 or the '544 Patent could be used as part of a dosing regimen with loading doses because "[f]unctionally, they're the same," (Werm. Tr. 326:6–13, 327:3–8), even though the WO'384 formulation would have been preferred. (FF 194, 200).

342. A POSA would have been motivated to use the teachings of the '548 Regimen with the formulations of the '544 Patent and WO'384 because all three were "trying to treat patients with schizophrenia" using "long-acting injectables" of paliperidone palmitate, and all three references had ties to Janssen. (Werm. Tr. 318:20–319:4).

343. Based on the '544 Patent, WO'384, and/or '548 Regimen, a POSA would have been especially motivated to select 150 mg-eq. as the first loading dose because she "would be motivated to use the maximum effective and safe dose" to achieve rapid loading. (Werm. Tr. 321:1–22, 426:2–8).

344. A POSA would know that "150 milligrams is actually not a very high dose". (Kahn Tr. 2447:8–23; Sinko Tr. 2106:13–17; FF 177).

345. A POSA would have known that 150, 100, or 50 mg-eq. could be used as the second loading dose because they were all shown to be reasonably safe and effective. (Werm. Tr. 474:2–6, 475:1–9; FF 177, 208, 219).

346. But a POSA would have been especially motivated to select a 100 mg-eq. dose for the second loading dose because paliperidone is already present in the blood, and a lower dose would "avoid this excessive accumulation." (Werm. Tr.

322:19–323:1; FF 254).

347. After selecting the loading doses, a POSA would have been motivated to follow the monthly dosing taught by the WO'384—amounts between 25–150 mg-eq. "as needed" in the deltoid or gluteal—as that was the most refined disclosure of monthly maintenance dosing of paliperidone palmitate. (FF 177, 201, 208, 219).

348. A POSA would have had a reasonable expectation of success in using loading doses for paliperidone palmitate, generally, because a "loading dose strategy was known to a [POSA] prior to 2007" "in the context of long-acting injectables for the treatment of schizophrenia." (Sinko Tr. 1790:23–1791:9; FF 242, 253, 260).

349. A POSA would have had a reasonable expectation of success in selecting 150 and 100 mg-eq. for the Days 1 and 8 injections, respectively, because these doses were used in a Phase III trial, which a POSA would know is intended to confirm safety and efficacy in a larger patient population and expected to work. (Werm. Tr. 316:17–317:2; Verm. Tr. 758:6–25; Gopal Tr. 1124:11–20).

350. A POSA would not need individual PK data to reasonably expect that all of the doses used in the '548 Regimen are effective; a POSA was "taught what dosing ranges are effective" in WO'384: "25 to 150 [mg-eq.]" (Werm. Tr. 322:7–13).

351. A POSA would have had a reasonable expectation of success in selecting 150 and 100 mg-eq. for the injections on Days 1 and 8 because the total loading dose amounts in the '548 Regimen amounted to "300" mg-eq. (2, 150 mg-eq. doses) and

"200" mg-eq. (2, 100 mg-eq. doses). "So if 300 [mg-eq.] loading doses and 200 [mg-eq.] loading doses are stated to be safe and effective, then ergo, something in between them would be safe and effective." (Werm. Tr. 321:1–322:6).

352. Applying the calculations of Ereshefsky, a POSA would reasonably expect that 20 times the 12 mg maximum oral dose of paliperidone is 240 mg paliperidone, which could be approximated by splitting into 150/100 mg-eq. loading doses. (Werm. Tr. 557:16–22).

353. It would have been obvious to a POSA to administer 150/100/100/100 mg-eq. paliperidone palmitate on days 1, 8, 36, and 64 respectively, each in the deltoid, because "it'd be reasonable" based on the available prior art. (Werm. Tr. 324:14–325:9, FF 311–313, 343, 347).

354. A dosing regimen of 150/100/100/100 mg-eq. paliperidone palmitate administered into the deltoid on days 1, 8, 36, and 64 falls within the scope of the dosing regimen of independent claim 1. (Werm. Tr. 325:18–326:3).

355. Obviousness of the Asserted Claims does not require a POSA to expect a dosing regimen 150/100/100/100 mg-eq. paliperidone palmitate on days 1, 8, 36, and 64 in the deltoid is the optimal dosing regimen, but a POSA would "be able to figure out what an optimal dosing regimen would be." (Sinko Tr. 2202:9–19).

356. A POSA would "have been able to, given the resources, run a clinical trial similar to the one observed in Protocol '548." (Sinko Tr. 2197:5–16, 21–24).

4. Selecting Injection Site

357. A POSA looking for "fast onset of effect" would have been motivated to select the deltoid because "POSAs knew that the rate of absorption" in the deltoid "is faster . . . than if made into the gluteus" and "because it's the easiest to access" in that "[y]ou generally don't have to disrobe." (Werm. Tr. 323:19–324:11; Kohler Tr. 1960:6–10; Kahn Tr. 2311:3–21; Gopal Tr. 1180:18–25; FF 225, 230).

358. A POSA would have had a reasonable expectation of success of administering into the deltoid, generally, because it is one of "the two most common" injection sites. (Sinko Tr. 1719:15–17; Werm. Tr. 280:16–21).

359. A POSA would have had a reasonable expectation of success of administering the paliperidone palmitate into the deltoid because other prior art studies had shown that paliperidone palmitate had been injected into the deltoid. (DTX-98; DTX-100).

360. Specifically, NCT00119756, another Phase III J & J study published on ClinicalTrials.gov, hypothesized "that there will be no difference in safety and tolerability between buttock injection compared to shoulder injection" for paliperidone palmitate. (DTX-100.0001).

361. The '548 Regimen's use of the gluteal as the injection site would not have discouraged a POSA from administering paliperidone palmitate to the deltoid, because the goal was not related to testing different injection sites. (FF 221).

362. Cleton 2008 would not have discouraged a POSA from administering

paliperidone palmitate to the deltoid, because those studies only discussed results (such as pain score or fluctuation index) ***relative*** to the gluteal; there is no suggestion that any of the ***total*** values were high enough to teach away from deltoid injections.

5. Modifying Formulation Elements

363. A POSA would know that if the ingredients and concentrations of two formulations are the same, they will have the same pH. (Sinko Tr. 2156:1–6).

364. A POSA would "be able to adjust the pH of an aqueous solution," (Sinko Tr. 1724:7–15), and use buffers to reach a pH of 7–7.5 (Sinko Tr. 1727:20–1728:5, 1728:19–24).

6. Modifying Particle Sizes

365. A POSA would have known that particle size of an injectable aqueous nanoparticle suspension is a result-effective variable, (Sinko Tr. 1779:22–1780:1), and naturally motivated to optimize the particle size through routine procedures.

366. A POSA would have known that milling particles is a "standard process[] that [is] used in pharmaceutics," (Werm. Tr. 294:20–25), and could mill to a specific size. (*Id*.; Sinko Tr. 2145:17–24; 1781:17–19).

367. A POSA could "experiment with different particle sizes to obtain a pharmacokinetic profile that he or she desired." (Sinko Tr. 1778:15–18).

368. A POSA would know how to create particle sizes consistent with either Formulations "B and C [from the '544 Patent] that had a d50 of 1380, or 740

nanometers." (Werm. Tr. 297:9–16).

369. A POSA "could choose to mill, instead of four or seven hours, could choose to mill five hours." (Sinko Tr. 1781:20–23).

370. A POSA would have sought to strike a balance between milling time and the desired properties attributed to particle size, as longer milling times increase total manufacturing time and cost. (FF 365, 367).

B. Obviousness of the Renal Dosing Regimen

371. Claims 10 and 13 differ from Claim 2 as to "the amount of drug" being administered. (Werm. Tr. 327:22–328:7).

372. The '591 Application, Cleton 2007, and/or the Invega ER Label would have provided a POSA a motivation to modify an obvious dosing regimen for patients with normal renal function to reduce the dose for patients with renal impairment, with a reasonable expectation of success in doing so. (FF 271–81).

373. A POSA would know that renally-impaired patients, who cannot clear drugs as efficiently through the kidneys, risk higher exposure to paliperidone, (Werm. Tr. 330:7–12; Kohler Tr. 1933:19–1934:5), which would motivate a POSA to reduce the amount of paliperidone administered compared to patients with normal renal function. (*See, e.g.*, Samtani Tr. 1388:3–21).

374. For instance, the label for Risperdal Consta recommends a dose of 25 mg every two weeks for patients for normal renal impairment, but a dose of 12.5 mg for

patients with impaired renal function, which is a 50 percent reduction. (Kahn Tr. 98:10–17; DTX-408.0031–0032).

375. The Invega ER Label likewise recommends a dose of 12 mg paliperidone daily for patients with normal renal function, but 6 mg daily for patients with mild renal impairment, again a 50 percent reduction. (FF 282, 283).

376. It would have been obvious to a POSA to administer 150/150/100/100 mg-eq. paliperidone palmitate into the deltoid on Days 1, 8, 36, and 64, respectively, to patients with normal renal function. (Werm. Tr. 327:22–328:7; FF 345).

377. It would have further been obvious to a POSA, based on the '591 Application, Cleton 2007, and/or the Invega ER Label, to reduce the dose of paliperidone by about 50% for patients with renal impairment, thereby producing a dosing regimen of 75/75/50/50 mg-eq. paliperidone palmitate, injected into the deltoid on Days 1, 8, 36, and 64 respectively. (Werm. Tr. 332:21–333:12).

378. A dosing regimen of 75/75/50/50 mg-eq. into the deltoid on Days 1, 8, 36, and 64 falls within the scope of claims 10 and 13. (Werm. Tr. 333:15–20).

379. Dr. Sinko improperly looked to Janssen's internal process in opining on the non-obviousness of claims 10 and 13, stating that Dr. Samtani's testimony informed him that "given the patient level data and the variability in the data that you would see, coming up with different dose reductions are very important and you need to relate them to this granular level of patient data." (Sinko Tr. 1588:10–18).

C. Range of Days to Administer Each Dose

380. "[T]he notion of . . . treat[ing] a person on a different day outside of protocol is common." (Werm. Tr. 414:9–16; Kahn Tr. 91:20–92:2, 2312:25–2313:13).

381. A POSA would know that "[p]atients have real-life situations to deal with," and may not be able to come in for their "monthly injection exactly at one month." (Samtani Tr. 1381:8–1382:3).

382. When an antipsychotic LAI is prescribed "once a month," doctors recognize that "a month is not necessarily 30 days," so "it can be a little less, or a few days more." (Kahn Tr. 91:16–92:2; *see also* Werm. Tr. 335:14–22).

383. A POSA would know that a sustained-release formulation can be administered several days before or after the prescribed day of administration because "blood levels change with [LAIs] pretty slowly," "so from one day to the next, there is not going to be a great change" in the concentration of drug in the blood. (Werm. Tr. 335:14–22; *see also* Samtani Tr. 1381:8–1382:3).

384. A POSA would have been motivated to administer, for instance, the obvious Day 8, 36, and 64 doses from the '548 Regimen on days other than Day 8, 36, or 64, respectively, to accommodate patient and health care professional schedules. (Werm. Tr. 414:9–16; Kahn Tr. 91:20–92:2; 2312:25–2313:13).

385. A POSA would have had a reasonable expectation of success of dosing on Days close to, but not exactly, Days 8, 36, and 64, respectively, because "it's

unlikely that the blood level change from one day to the next is going to have any change in the therapeutic outcome." (Werm. Tr. 335:23–336:17; 336:21–23 (noting same is true for patients with renal impairment)).

D. Dr. Sinko's Opinion of Non-Obviousness is Based on an Erroneous Understanding of the Claims

386. In rendering his opinion on non-obviousness, Dr. Sinko fundamentally misunderstood the scope of the claims.

387. Dr. Sinko erroneously read in an "efficacy" or "treatment" result or outcome requirement to conclude the claims are non-obviousness. (Sinko Tr. 1676:5–10 (agreeing that if "*the patient is treated*, then [the claim] would be satisfied."); Sinko Tr. 1686:4–16 (stating that the regimen must "*successfully treat the patient*"); Sinko Tr. 1690:22–24, 1691:16) (emphasis added)).

388. None of the Asserted Claims contain any term that requires the claimed dosing regimen to be effective in "a patient in need of treatment." (DTX-1/PTX-1 at cls. 2, 10, 13, 20, 21; Samtani Tr. 1425:19–22).

389. Each Asserted Claim would be met by administering doses of the claimed amount, at the claimed time, to the claimed site, even if the regimen were ineffective on the particular subject. (DTX-1/PTX-1 at cls. 2, 10, 13, 20, 21).

390. "[A]ll patients who are dosed with Invega Sustenna according to the label don't necessarily respond," (Sinko Tr. 1663:1–7), even if administered a dosing regimen consistent with claim 2, (Sinko Tr. 1676:5–10).

391. The ’544 and ’843 Patents both had claims that expressly claimed and enabled administering “therapeutically effective” amounts of paliperidone palmitate. (DTX-54/PTX-55 at cls. 1, 7; DTX-71 at cls. 1, 10).

392. None of the Asserted Claims contain any term that would require the claimed dosing regimen to produce any particular blood levels. (’906 Patent, cls. 2, 10, 13, 20, 21; Samtani Tr. 1423:5–6, 9).

393. Dr. Sinko improperly read in a requirement that the formulation administered using the dosing regimen of claim 2 be the same as IS. (Sinko Tr. 1680:11–23).

394. Dr. Sinko also improperly read in the particle size limitation of claim 19 into claim 2 when opining on the non-obviousness of claim 2, but claim 2 does not require a nanoparticle suspension. (Sinko Tr. 1653:13–21).

395. Dr. Sinko’s conclusion that a POSA would be motivated to modify the prior art to arrive at the claimed dosing regimen only if there were safety and efficacy data available is incorrect. (*See* Sinko Tr. 1580:2–16, 1589:13–1590:4).

396. As part of his non-obviousness opinion, Dr. Sinko erroneously considered a lack of pharmacokinetic data in the prior art is “important” to arrive at “an *effective* dosing regimen.” (Sinko Tr. 1583:24–1584:16) (emphasis added).

397. The prior art taught doses that were effective, (*see* FF 177, 208), or would be expected to be effective, (FF 219), which obviates the need for individual PK data.

398. Dr. Sinko erroneously concluded that a POSA must have “a reasonable

expectation of finding an optimal dosing regimen." (Sinko Tr. 1715:12–16).

399. Dr. Sinko erroneously "underst[ood] the claims to require the dosing regimen [] result in rapid efficacy and long-term efficacy." (Sinko Tr. 1657:20–1658:3, 1658:4–20).

400. The "literal[]" words "rapid efficacy" or "long-term efficacy" do not appear in claim 2. (Sinko Tr. 1655:3–6, 1657:11–13).

401. None of the Asserted Claims exclude use of oral supplementation, an oral tolerability test or oral run-in. (DTX-1/PTX-1 at cls. 2, 10, 13, 20, 21; Samtani Tr. 1422:12–14; Kohler Tr. 1944:5–7).

402. None of the Asserted Claims require the dosing regimen be effective in any number of patients. ('906 Patent, cls. 2, 10, 13, 20, 21; Samtani Tr. 1424:18–19).

403. None of the Asserted Claims preclude refrigeration. (Kohler Tr. 1944:8–10).

404. Dr. Sinko's POSA lacked ordinary creativity and would have applied the prior art rigidly, like an automaton. (*See, e.g.*, Sinko Tr. 1569:18–1570:9; 1778:24–1779:8; 1781:20–1782:13; 1782:14–1783:3; 1785:7–13; 1790:1–3, 7–22).

XI. SECONDARY CONSIDERATIONS

405. Dr. Sinko only offered opinions on "copying and failure of others" as evidence of non-obviousness, both of which relied on Teva's ANDA product. (Sinko Tr. 1610:3–7; 2165:5–20).

406. Dr. Sinko did not opine that "that the claimed dosing regimen gives superior

efficacy to other possible dosing regimens that aren't claimed[.]" (Sinko Tr. 1700:22–1701:1).

407. Dr. Kohler did not testify as to the existence of any long-felt need for a dosing regimen of paliperidone palmitate.

A. No Nexus Between The Claims And Secondary Considerations

408. Plaintiffs failed to provide sufficient evidence that any secondary consideration of non-obviousness shared a nexus to the novel features of the claims.

409. Dr. Sinko only offered opinions that IS practices claims 1, 20, and 21 of the '906 Patent. (Sinko Tr. 1611:17–1612:8).

410. Plaintiffs failed to provide any evidence that any secondary consideration of non-obviousness shares a nexus to claims 10 and 13.

411. Dr. Kohler did not know whether health care providers administer IS consistent with the label, or whether other dosing regimens are equally effective. (Kohler Tr. 1956:25–1957:24, 1959:14–1960:5).

412. REDACTED

REDACTED

REDACTED

REDACTED

413. The IS Label instructs that patients may receive the second loading dose on Days 4–12. (DTX-11.0002; Kohler Tr. 1990:6–11). If a patient were administered IS on Day 4, 5, 11, or 12, consistent with the IS label, that patient would not be receiving the claimed dosing regimen. (Kohler Tr. 1990:25–1991:14; 1991:22–1992:1; Kahn Tr. 2446:7–13).

414. Plaintiffs failed to provide any evidence that any secondary consideration of non-obviousness shares a nexus to the d50 range required by claims 20 and 21.

B. No Reliable Evidence of Commercial Success

415. "[T]he alleged inventions of the '906 patent" have not "been commercially successful." (Hofmann Tr. 2777:3–6).

1. Janssen's Blocking Patents

416. As of 2007, those "seeking to develop a drug" would know "that Janssen had five antipsychotic products on the market already," and "had been active in [that] market since 1967," (Mulhern Tr. 2710:11–22), which would have dissuaded or even

blocked others from entering that market. (Hofmann Tr. 2743:14–22).

417. Blocking patents exist where "the commercialized product is protected by a patent" having "a scope that would preclude or limit competition." (Hofmann Tr. 2740:22–2741:3).

418. At least the '556, '843, and '544 Patents, each of which was listed on the Orange Book and owned by Janssen, blocked competitors from developing paliperidone palmitate products and dosing regimens. (Hofmann Tr. 2744:13–15, 2745:20–23, 2746:1–3; DTX-193.1109; DTX-140; DTX-141).

419. Mr. Hofmann's understanding of the scope of the blocking patents comes from "the patents themselves," Janssen's entries in "the Orange Book," and Dr. Sinko's testimony at trial; the opinions in Dr. Wermlings's expert report were neither "required" nor "necessary." (Hofmann Tr. 2791:18–25, 2863:20–2864:2).

420. Mr. Hofmann's testimony at trial regarding Janssen's blocking patents is credible and based on appropriate foundation.

421. Janssen did not present evidence that the '556, '843, or '544 Patents were ever challenged during their lifetimes, (Mulhern Tr. 2707:3–8), or that Janssen was ever willing to, or did, license those Patents, (*id.* at 2707:12–13).

422. Whether other companies could develop products using other drug compounds is irrelevant and "the absolute wrong inquiry" for purposes of evaluating whether Janssen's blocking patents prevented others from "conceiv[ing] of the

dosing regimen contained in the '906 patent with respect to paliperidone palmitate." (Hofmann Tr. 2756:7–14).

a. '952 Patent

423. Claim 1 of the '952 Patent recites the chemical name for paliperidone.[2] (*Compare* DTX-803, cl. 1, *with* Sinko Tr. 2147:1–7; DTX-72/PTX-66 at 1:15–17), and claim 3 recites "a method of treat[ment]" for "psychotic diseases" using paliperidone. (DTX-803, cl. 3).

424. The '952 Patent, owned by Janssen excluded others from using the paliperidone compound from Oct. 27, 1992 to Oct. 27, 2012. (DTX-803.0001).

b. '556 Patent

425. The '556 Patent is a blocking patent that was enforceable from October 19, 1993 to October 15, 2013, (DTX-69.0001; DTX-193.1109), and existed for many years before and after the filing date of the '906 Patent. (Hofmann Tr. 2753:5–17).

426. Claim 1 of the '556 patent covers paliperidone palmitate, (DTX-69 at cl. 1 (claiming "$C_{2–20}$ alkanoic esters" of the chemical name for paliperidone; Sinko Tr. 2271:13–16, 2153:6–2153:18, 2272:16–19; FF 423; *see also* DTX-54/PTX-55 at 3:56–64 ("C_{15}" ester chain is paliperidone palmitate)), and claim 3 covers a method of treating "psychotic diseases," by administering "the compound of claim 1."

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[2] Specifically, the claim recites, in part, : "[a] compound selected from the group consisting of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-l-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one."

(DTX-69 at cl. 3; Sinko Tr. 2272:22–2273:2).

427. Janssen listed the '556 Patent in the Orange Book, representing it covered the IS drug substance and product (paliperidone palmitate), and a method of using IS to treat schizophrenia. (DTX-157.0002; DTX-193.1109; Hofmann Tr. 2747:9–18, 2788:25–2789:3, 2796:20–25, 2797:25–2798:1, 2803:1–10; Mulhern Tr. 2697:4–7).

428. Janssen offered no evidence disputing the scope of the '556 Patent claims cover paliperidone palmitate.

429. The '556 Patent serves "as a very strong economic block" for anyone to use paliperidone palmitate. (Hofmann Tr. 2748:21-25, 2749:1–3, 2753:20–21; Mulhern Tr. 2704:15–18).

430. In order to practice the '906 Patent claims, a POSA must use paliperidone palmitate. DTX-1/PTX-1 at cls. 1, 4, 8, 11 (all claiming "paliperidone palmitate")).

431. The '556 Patent prevents "anyone other than Janssen from coming up with uses, coming up with formulations, coming up with dosing regimens with respect to the paliperidone palmitate other than Janssen." (Hofmann Tr. 2754:3–8).

c. '843 Patent

432. The '843 Patent is a blocking patent that was enforceable from Jun 20, 2000 to May 12, 2017. (Mulhern Tr. 2705:13–17; DTX-71.0001; DTX-193.1109).

433. None of the named inventors of the '843 Patent overlap with the named or purported inventors of the '906 Patent. (*See* DTX-71 at 1).

434. Claim 1 of the '843 Patent covers a generic aqueous "depot formulation" of paliperidone palmitate for intramuscular injection. (DTX-71.0005–0006 at cl. 1 (claiming "a 9-hydroxyrisperidone fatty acid ester" with a "straight $C_{9–19}$alkyl radical"; *see, e.g.*, DTX-54/PTX-55 at 3:56–64 ("C_{15}" chain is palmitate)).

435. Claim 10 of the '843 patent covers "[a] method of treat[ment]" for "schizophrenia" by administering "the composition of claim 1." (DTX-71 at cl. 10).

436. Janssen listed the '843 Patent in the Orange Book, telling the public that the patent claimed the IS drug product, and that claim 10 of the '843 Patent claims a method of using IS in the treatment of schizophrenia. (DTX-159; DTX-193.1109; Hofmann Tr. 2750:3–7).

437. Thus, the '843 Patent indisputably covers generic aqueous formulations of paliperidone palmitate. (Sinko Tr. 2272:16–19; Mulhern Tr. 2698:24–2699:2; *see also id.* at 2698:3–6).

438. Janssen offered no evidence disputing the scope of the '843 Patent.

439. The '843 Patent would block others from developing an aqueous formulation of paliperidone palmitate, or using that formulation to treat schizophrenia. (FF 434; *see also* Hofmann Tr. 2740:12–21, 2750:12–20).

d. '544 Patent

440. The '544 Patent is a blocking patent that was enforceable from April 29, 2003 to November 10, 2018. (DTX-54/PTX-55 at 1; DTX-193.1109).

441. Janssen listed the '544 Patent in the Orange Book as covering IS prior to its expiration with use code U-543. (Sinko Tr. 1748:12–14; DTX-193.1109).

442. Claim 1 of the '544 Patent covers an aqueous paliperidone palmitate nanoparticle formulation. (DTX-54/PTX-55 at 9:65–10:30; Sinko Tr. 1763:9–19, 1534:7–13; Woodrow Dep. 103:13–15, 108:18–22; Werm. Tr. 275:3–16; DTX-160 § 3.1).

443. Claim 7 of the '544 Patent depends from claim 1 and is directed to a method of treating schizophrenia by "administering a therapeutically effective amount of" the composition, paliperidone palmitate, (Sinko Tr. 1764:21–1765:1, 14–15; Werm. Tr. 290:18–291:3; DTX-54/PTX-55 at 10:58–65).

444. Janssen represented to the FDA (DTX-160) and stipulated here that "Claim 7 . . . of the '5[4]4 [patent] covers Invega Sustenna®." (Sinko Tr. 1770:1–3).

445. "[T]he '544 patent adds yet another layer to the, really, patent fortress that Janssen has buil[t] up around the use of paliperidone palmitate for the treatment of schizophrenia and schizoaffective disorder." (Hofmann Tr. 2752:5–8).

e. Teva Manufacturing Patent

446. "[I]t's not atypical for ANDA filers to . . . try and get patents, like manufacturing processes," in order to "chill the entrance by other generic competitors." (Hofmann Tr. 2831:13–17).

447. Teva's manufacturing patent does not detract from the fact that the '556, '843,

and ’544 Patents blocked competitors from developing the claims of the ’906 Patent.

448. The safe harbor from patent infringement for research development does not apply to commercialization of a product. (Hofmann Tr. 2824:3–8).

2. Nexus

a. Sales and Revenue Not Attributable to the Claimed Dosing Regimen

449. In presenting sales data as evidence of commercial success, Ms. Mulhern failed to discount sales to patients that did not receive the claimed dosing regimen. (Mulhern Tr. 2642:7–12)).

450. REDACTED

REDACTED

451. Ms. Mulhern also failed to discount sales to patients who received the second loading dose on days that did not fall within the scope of the claimed days 6–10, such as days 4, 5, 11, or 12 (FF 413). (Mulhern Tr. 2642:21–23).

452. Ms. Mulhern failed to account for the fact that “Janssen assumes that one unit of Invega Sustenna® equates to 28 days of treatment,” but that “some units of Invega Sustenna® account for only seven days of treatment,” for instance, “for the loading doses.” (Mulhern Tr. 2644:6–13).

453. Ms. Mulhern also failed to discount sales to patients with renal impairment who were administered the dosing regimen pursuant to the label (i.e., 100/75 mg-eq. loading doses), which fall outside the scope of the claims (i.e., 75/75 mg-eq. loading

doses). (Mulhern Tr. 2646:15–19).

454. Ms. Mulhern did not consider the prior art in her analysis; she based her opinions entirely on Janssen's technical experts, (Mulhern Tr. 2613:22–24, 2667:10–18), and "the extent to which the patented benefits were thought to be differentiators by healthcare providers," without tying those "differentiators" to the novel features of the claims. (*Id*. at 2589:16–2590:12).

b. Invega Sustenna's Competition from 2009–2013

455. Just before IS launched, there were "two generic competitors" of injectables—fluphenazine decanoate and haloperidol decanoate—and "one branded competitor . . . Risperdal Consta." (Mulhern Tr. 2663:3–8, 2663:20–23).

456. Because "generics don't typically tend to engage in active marketing of their generic products," (Mulhern Tr. 2662:22–2663:2), "revenue is going to skew more heavily to branded and promoted products." (Hofmann Tr. 2835:19–23).

457. "Janssen stopped actively marketing Risperdal Consta® in 2013 or 2014," (Mulhern Tr. 2663:25–2664:2), making it impractical to obtain, (Kohler Tr. 1918:8–12) and [redacted] (Tewell Dep. Tr. at 86:13–19, 86:23–87:5).

458. The lack of marketing and declining sales of Risperdal Consta contributed to IS's sales. (Hofmann Tr. 2844:23–2845:4).

459. Yet "as of the first quarter of 2015, Risperdal Consta® still held about an 18 percent market share." (Mulhern Tr. 2657:7–11, 2657:22–24).

460. Abilify Maintena, "the next LAI, did not launch until the first quarter of 2013," so IS "was on the market for some years" without branded competitors except Risperdal Consta. (Mulhern Tr. 2665:9–14, 2665:17–18).

461. Abilify Maintena's revenue, however, has "consistently increased from the time of its launch until . . . 2/4/2018, at least." (FF 493).

c. Janssen's Marketing Drives Commercial Performance of Invega Sustenna

462. Janssen's "sophisticated" and "commercial marketing strategies" "benefit Invega Sustenna® and explain the marketplace performance," which is "unrelated to the particular dosing regimen or the particular claims that are in the '906 patent." (Hofmann Tr. 2769:19–22; Mulhern Tr. 2614:18–20).

463. [redacted]

464. Janssen has executed a strategy of "continually mov[ing] from oral to a long-acting injectable version of [its] products," including "many different molecules over many decades." (Hofmann Tr. 2761:16–2762:13; DTX-287.0032; FF 67).

465. IS also "benefits from the long, long history that [Janssen's] reputation has in the neuroscience field and that its sales force has with prescribers who work in this space." (Hofmann Tr. 2759:17–22).

466. Janssen's "portfolio optimization strategy," or "lifecycle management," uses "targeting, messaging, and sampling to essentially leverage short-acting

paliperidone and risperidone molecules to grow Invega Sustenna®." (Hofmann Tr. 2764:1–3, 2764:8–12; DTX-291, slide 26).

467. Janssen leveraged prescriber familiarity with risperidone and paliperidone in selling IS. (Hofmann Tr. 2757:14–2758:1).

468. Janssen uses "sampling" (providing free samples to physicians to "encourage use of a pharmaceutical product") (Hofmann Tr. 2770:18–24) to produce "a tremendous uptick" in prescriptions. (Hofmann Tr. 2771:2–4; PTX-397, slide 19; Mulhern Tr. 2688:17–22).

469. As of 2016, "the primary source of Invega Sustenna®," "was oral risperidone and paliperidone." (Mulhern Tr. 2679:1–13). Indeed, "nearly half of the Invega Sustenna® prescriptions[ ] are coming from Risperdal or risperidone products, and paliperidone, which would be the short-acting Invega product." (Hofmann Tr. 2765:2–7; DTX-288, slide 11).

470. Janssen utilizes a sales force of "more than 500 [] personnel that are visiting physicians and promoting Invega Sustenna," (Hofmann Tr. 2770:10–14; Tewell Dep. Tr. at 37:8–10), which helps drive sales. (Hofmann Tr. 2771:20–2272:1).

471. [redacted] To prescribe the Invega Trinza® product to their patient, doctors "are required to have the patient buy Invega Sustenna®." (Mulhern Tr. 2674:13–15). Indeed, "26 percent of the growth in Invega Sustenna® was being

driven by the launch of Invega Trinza®." (Hofmann Tr. 2769:11–13).

472. Janssen "spent more than $1.1 billion on sales and marketing efforts from 2011 to 2018" for IS. (Hofmann Tr. 2772:2–6). Such expenditures are "unrelated to the claims of the patent-in-suit." (*Id*. 2773:17–23).

473. The sales data that Ms. Mulhern presented did not "reflect the marketing" expenditures." (Hofmann Tr. 2834:6–17).

474. Janssen did not provide "access to [total marketing and promotional expenditures] from before 2011," which is "important because . . . Invega Sustenna® launched in 2009" and "typically, pharmaceutical companies will have some of their highest expenditures at launch;" (Hofmann Tr. 2772:7–13); nor access to such data from 2018 and 2019, which would only increase the "billion-plus dollars even further." (*Id*. 2772:21–2773:1).

475. Ms. Mulhern did not compare, analyze, or otherwise account for sales attributable to marketing expenditures. (Mulhern Tr. 2665:2–8).

476. From 2015 to 2018, "Janssen gave away $2.5 billion in discounts and rebates in order to motivate prescribing behavior and use of Invega Sustenna®." (Hofmann Tr. 2775:6–7, 2775:14–17).

477. All together, Janssen has spent "easily in the excess of $4 billion" to drive sales of Invega Sustenna® which doesn't have anything to do with the '906 patent." (Hofmann Tr. 2776:12–24; DTX-47).

C. No Long-Felt Need For the Combined Benefits

478. Janssen has not presented any evidence that there was a long-felt and unmet need in the medical community that is satisfied by IS (Kahn Tr. 2410: 8–17; Kohler Tr. 1910:7–1912:13).

479. Dr. Kohler did not provide "any testimony that would indicate there was a long-felt but unmet need for the dosing regimen claimed in the '906 Patent." (Kahn Tr. 2298:11–15).

480. IS has not "change[d] the way schizophrenia patients [a]re clinically treated[.]" (Kahn Tr. 2297:14–20).

481. For schizophrenia, "the first choice of medication is oral medication," not LAIs. (Kohler Tr. 1943:10–20; Kahn Tr. 2303:8–2304:14). Only those who "are not compliant or not adherent" are considered for LAIs. (Id.).

482. Oral antipsychotics remain the top choice for patients and maintain an overwhelming majority share of the overall antipsychotic market. (Mulhern Tr. 2653:15–23; Hofmann Tr. 2742:12–14).

483. The testimony Dr. Kohler provided on IS's benefits is anecdotal evidence based on his personal experience, and is entitled to little weight. (Kahn Tr. 2298:21–2300:2, 2308:3–13, 2313:22–2314:3, 2314:16–22; Kohler Tr. 1949:11–17, 1963:21–25, 1999:23–2001:21).

484. "[D]rugs that were available [in 2007] cover the claims or benefits that Dr.

Kohler" alleged, including: fluphenazine decanoate (Prolixin Decanoate); haloperidol decanoate (Haldol Decanoate); flupenthixol decanoate (Fluanxol); pipotiazine palmitate (Piportil Depot); risperidone (Risperdal Consta); zuclopenthixol decanoate (Clopixol); fluphenazine enanthate (Prolixin enanthate); and clopenthixol decanoate (Sordinol Depot). (Kahn Tr. 2300:3–2302:8; *see also* DTX-147; DTX-149; DTX-146; DTX-178; DTX-194; DTX-408).

485. Haloperidol decanoate remains popular, with at least 34% market share based on days of treatment, higher than the market share of IS. (Mulhern Tr. 2583:1–10; *see also* Mulhern Tr. 2655:17–21; PTX-806B at 30–37).

1. Prior Art Second-Generation Antipsychotics

486. Risperdal, Risperdal Consta, olanzapine, and Invega ER are second-generation antipsychotics available prior to 2007. (Kahn Tr. 2316:9–2317:15).

487. It cannot "be claimed that second-generation antipsychotics are safer than first-generation antipsychotics." (Kahn Tr. 2316:9–2317:15).

2. Rapid Efficacy

488. The second claimed loading dose in the '906 Patent does not contribute to rapid efficacy, because rapid efficacy should occur before the second injection on Days 6–10. (Kahn Tr. 2306:25–2308:2).

489. Efficacy is measured by a "PANSS" score (or "[p]ositive and negative symptom scale") in which a heath care professional asks a patient 30 questions "that

gives you an idea of how bad or how good the patient is doing," with the goal of scoring "as low as possible." (Verm. Tr. 774:18–775:10, 14–16).

490. Janssen did not present any PANSS data before Day 8 that would indicate rapid efficacy. (Kahn Tr. 2306:25–2308:2; Verm. Tr. 863:23-25).

491. "[O]ther commercial products that were available in 2007," such as fluphenazine decanoate, were rapidly effective. For fluphenazine decanoate, "the label indicates that its first effect can be seen after 24 hours, and then the antipsychotic effect a few days later, but certainly within a week." (Kahn Tr. 2309:4–12; DTX-147.0005).

492. Fluphenazine decanoate is administered intramuscularly, which a physician would understand to mean "the gluteal muscle or the deltoid." (Kahn Tr. 2310:25–2311:21).

3. No Oral Supplementation/Run-In

493. The record evidence does not demonstrate that oral run-in is considered a drawback; to the contrary, "Abilify Maintena," another second-generation "orally supplemented drug," has consistent sales growth. (Mulhern Tr. 2669:21–2670:2).

494. Very few prior LAIs require oral run-in. (Kahn Tr. 2305:13–19; DTX-147.0005; DTX-149.0012–0013; DTX-146.0012; DTX-178.0001).

495. Likewise, "oral supplementation is actually pretty rare in the use of long-acting injectables." (Kahn Tr. 2305:5–12; DTX-147.0005; DTX-149.0012–0013;

DTX-146.0012; DTX-178.0001).

496. The IS label instructs pre-retreatment with oral paliperidone or risperidone, (DTX-11.0001, 0003), which constitutes oral run-in.

4. Prior Art Monthly Injectables

497. Prior art antipsychotics such as fluphenazine decanoate, haloperidol decanoate, zuclopenthixol decanoate, and pipotiazine palmitate were administered monthly. (Kahn Tr. 2304:21–2305:4; DTX-147.0005; DTX-149.0013; DTX-178.0001; DTX-194.0001).

5. Balance of Safety and Efficacy

498. All prior commercial LAIs have an optimal balance of safety and efficacy, as "a drug by definition is only allowed on the market if it has a critical balance between safety and efficacy." (Kahn Tr. 2314:23–2315:14).

499. Although "second-generation antipsychotics induce less extrapyramidal or Parkinsonian symptoms than first-generation antipsychotics, [] it's a question of degree"; second-generation antipsychotics "still do induce EPS and Parkinson's symptoms." (Kahn Tr. 2316:9–2317:15).

500. Extrapyramidal disorder ("EPS") is one of "the most common adverse reactions with Invega Sustenna." (Kohler Tr. 1961:20–25; Kahn Tr. 2319:8–12; DTX-11.0001 ("Adverse Reactions")).

501. There is no evidence "comparing EPS sy[mptoms] for IS to any first-

generation long-acting injectable medications." (Kohler Tr. 1963:20–25).

502. EPS symptoms are often "managed by giving other medications which are called 'anticholinergics'" or "benzodiazepines to reduce EPS[.]" (Kahn Tr. 2319:18–2320:4).

503. Second generation antipsychotic have their own set of side effects, including "considerable weight gain" and "akathisia," which is "a feeling of intense restlessness." (Kahn Tr. 2316:9–2317:15, 2320:5–20; Kohler Tr. 1964:3–20).

504. Despite the purported benefits provided by IS, Dr. Kohler "see[s] very limited benefit about switching [patients] to Invega Sustenna" if they are in "the chronic population, people who are maintained on Haldol Decanoate or Prolixin Decanoate." (Kohler Tr. 1917:20–1918:7). But "schizophrenia [is] almost by definition [] a chronic illness." (Kahn Tr. 2317:22–2318:18).

505. There is no evidence the claimed dosing regimen reduces injection site pain, which if anything "has to do with the suspension and with the formulation and with the volume that's injected." (Kahn Tr. 2306:11–17; Kohler Tr. 1946:20–25).

506. Injection site reactions are one of "the most common adverse reactions for Invega Sustenna." (Kohler Tr. 1963:16–19; DTX-11.0001).

6. Room Temperature

507. "Most of [the listed] long-acting injectables . . . could be stored at room temperature." (Kahn Tr. 2305:20–23; DTX-147.0006; DTX-149.0013; DTX-

146.0011).

508. "[T]he dosing regimen claimed in the '906 patent" has "nothing" "to do with the ability to store a product at room temperature." (Kahn Tr. 2305:24–2306:2).

7. Haldol Decanoate

509. The 2007 FDA-approved label for Haldol Decanoate instructed physicians to use a loading dose regimen of 20 times the patients' daily oral dose of Haldol. (Kohler Tr. 1966:25–1967:4; DTX-149 at 13).

510. The Haldol Decanoate label instructs that after the initial loading dose, successive doses of the drug should be reduced. (DTX-149 at 13).

511. The label for Haldol Decanoate provides a loading dose regimen that does not require oral supplementation.

512. The 2007 Haldol label instructs that "[i]f [] conversion requires more than 100 milligrams of haloperidol decanoate as an initial dose, that should be administered in two injections, i.e., a maximum of 100 milligrams initially, followed by the balance in three to seven days." (DTX-149 at 12–13; Kohler Tr. 1967:13–23).

513. Consistent with the 2007 Haldol label, if 20 times a patient's oral haloperidol dose were 180 mg, a patient would receive a dose of 100 mg on Day 1, and a second dose of 80 mg between Days 4 and 8. (Kohler Tr. 1967:24–1968:7).

514. In one clinical study, there was "no difference" in the rate of efficacy failure "between paliperidone palmitate and haloperidol decanoate." (Kahn Tr. 2412:9–23;

PTX-133 at 9 (page 213)). Rather, "participants in the PP group gained weight and those in the haloperidol decanoate group lost weight." (PTX-133 at 9 (page 213); Kahn Tr. 2443:8–2444:4).

8. "Dosing Windows"

515. IS's dosing windows are not a novel aspect of the '906 Patent.

516. "[M]ost antipsychotics, oral or long-acting, have a flexible dosing regimen" so that health care professionals can "adapt doses from lower to higher" or "reverse." (Kahn Tr. 2314:4–11; Kahn Tr. 2312:25–2313:13).

9. Clinical Studies Do Not Support the Purported Benefits of Invega Sustenna

517. Although the 2019 IS Label was revised to include a study (Study 6: SCH-3006, or the "PRIDE" study), (Kohler Tr. 2008:13–2009:2; PTX-627 at 51; DTX-11.0014), the study does not indicate whether patients received the claimed or an unclaimed dosing regimen. (Kohler Tr. 2012:22–2013:7).

518. The PRIDE study was also discussed in an article by Larry Alphs. (Kohler Tr. 2010:20–22; PTX-508 at 1 (p. 554)).

519. The PRIDE study required participants to have been incarcerated or in custody more than two times in the two prior years, and have been "released from their most recent custody within 90 days of the screening visit." (Kohler Tr. 2014:9–14; PTX-508 at 2 (p. 555)).

520. The PRIDE study compared IS to "all kinds of" oral antipsychotics, which is

a "logical problem[] with that study," (Kahn Tr. 2327:6–22), that fails to compare IS to any particular drug. (Kahn Tr. 2329:21–2330:24).

521. The PRIDE study failed to show any "significant differential impact on global clinical severity or time to re-hospitalization when compared to oral antipsychotics." (PTX-131 at 3). It "did not show that Invega Sustenna was superior to all the[] other oral antipsychotics in this particular group of patients in preventing rehospitalization, which is a proxy for adherence." (Kahn Tr. 2328:4–2329:9).

522. The PRIDE study "didn't show improved adherence. . . . [I]t showed less risk for incarceration." (Kahn Tr. 2326:12–17; Kahn Tr. 2327:23–2328:3).

523. The results of the PRIDE study are contradicted by the results of Janssen's "DREaM" study, which used the "same endpoint" to evaluate results. (Kohler Tr. 2008:13–2009:2; *compare* PTX-508 at 1 *with* DTX-857.0001; DTX-681 at 6).

524. Unlike the PRIDE study, the DREaM study was not limited to recently-incarcerated study participants. (Kohler Tr. 2014:21–24; DTX-857.0001–0002 (defining inclusion criteria)).

525. The DREaM study "demonstrated that the time to first treatment failure of paliperidone palmitate versus oral antipsychotics was not significant." (DTX-857; Kohler Tr. 1974:3–9). This means "paliperidone palmitate was not better than oral antipsychotics with respect to first treatment failure according to this study." (Kohler Tr. 1974:12–17; DTX-681).

D. No Evidence of Copying

526. The complete formulation for IS was available in the prior art. (FF 195–197).

527. "Teva is, as a generic, required by the FDA to establish bioequivalence." (Sinko Tr. 1616:1–5).

528. Teva's generic product is required to also "have the same ingredients" and "in the same amount" as IS. (Sinko Tr. 1620:5–16, 1620:5–16). This is known as qualitative (Q1) and quantitative (Q2) equivalence. (*Id.*).

529. [redacted]

530. Because particle size impacts the pharmacokinetics of an injectable formulation, [redacted]

531. On May 9, 2013, before Teva had filed its ANDA, Janssen submitted a Citizen's Petition to the FDA seeking enforcement of a heightened standard of bioequivalence that also accounted for particle size of generic versions of IS. (DTX-26.0015–0017, 0026–0031).

532. [redacted]

[redacted]

533. Teva's ANDA product is not probative of copying.

E. No Failure of Others

534. Janssen's only "failure of others" argument is [redacted]

535. [redacted]

536. [redacted]

537. [redacted]

538. Dr. Sinko considers studies a failure when they "fail[] to reach [expected] objective[s]," regardless of the reason. (*See, e.g.*, Sinko Tr. 1643:19–1644:1).

539. [redacted]

[redacted]

540. [redacted]

F. No Criticality or Unexpected Results

541. Neither Drs. Sinko nor Kohler offered an opinion on unexpected results related to the claimed dosing regimen of the '906 Patent. (Sinko Tr. 1610:3–7; Kahn Tr. 2298:7–10).

1. Janssen's Clinical Data Shows Other Doses, Dosing Regimens, and Injection Sites are Safe and Effective

a. Janssen's Early Phase I Studies

542. Janssen's first Phase I studies, BEL-1 and BEL-2, tested paliperidone palmitate formulations with a single injection. (PTX-380 at 1; PTX-381 at 1).

543. Another Phase I study, BEL-4, tested monthly administration of 50, 100 and 150 mg-eq. doses of paliperidone palmitate. (PTX-382 at 1; Verm. Tr. 848:16–25).

544. BEL-4 did not include any loading doses. (Verm. Tr. 854:10–17).

545. There were no "concerns about any of" the BEL-4 "regimens being unreasonable or unethical to give to patients at the time," (Verm. Tr. 849:15–23), even though Janssen lacked any data for multiple doses. (*See* FF 542).

546. BEL-4 showed that at least "50 percent of [the] subjects" reported plasma concentrations above the 7.5 ng/mL therapeutic threshold by Day 4 after a 50 mg-eq. dose, Day 3 for 100 mg-eq., and Day 2 for 150 mg-eq. (Verm. Tr. 852:1–11, 852:20–853:5, 854:1–9; PTX-382 at 81-83).

547. Many subjects who reached the therapeutic threshold by Day 5 stayed within a therapeutic window substantially between 7.5–40 ng/mL or 7.5–100 ng/mL until more than a month after the last dose. (*see* PTX-382 at 80–83).

548. BEL-4 shows that monthly injections of 50, 100, and 150 mg-eq. paliperidone palmitate, without loading doses, would be suitable for some patients. (FF 546-547).

549. Another Phase I study, BEL-7, tested "loading doses" very early in the development of paliperidone palmitate. (Verm. Tr. 854:22–24; PTX-165 at 1).

550. In the Day 1/Day 8 loading dose arm, subjects were given either 50 or 150 mg-eq. for both doses, which was considered "reasonable" by the development team, (Verm. Tr. 856:13–20; PTX-165 at 1), even though Janssen lacked any data for loading doses. (*See* FF 542, 543).

551. USA-3 tested injections of 25 or 150 mg-eq. paliperidone palmitate into the deltoid or gluteal on Days 1 and 8. (PTX-181 at 13, 21–22; Verm. Tr. 770:13–22).

552. Injections at both sites and both amounts was found to be "generally safe and well tolerated[.]" (PTX-181 at 87).

553. "Dr. Ereshefsky was a clinical co-investigator in this study." (Verm. Tr. 975:3–6; PTX-181 at 630).

554. Janssen initiated two other studies, PSY-1001 and 1004, utilizing deltoid injections just three to four months after the USA-3 study report was issued. (PTX-269 at 1, 16; PTX-674 at 1, 19; Verm. Tr. 802:22–25, 803:1–5, 975:12–20).

b. Early Efficacy Study

555. SCH-201 was a Phase II/III study that tested 50 and 100 mg-eq. paliperidone palmitate injections in the gluteal on Days 1, 8, and 36. (PTX-279 at 21, 24; Gopal Tr. 1053:9–23; Verm. Tr. 774:7–17).

556. The results were "fantastic," (Gopal Tr. 1054:2-8), and showed the median subject had a paliperidone blood plasma concentration in excess of 7.5 ng/mL, better than placebo by Day 8, (PTX-279 at 81, 190; Verm. Tr. 863:19–864:4), the earliest point efficacy (PANSS) was measured after injection. (PTX-279 at 37, Table 3).

557. SCH-201 is reported as a success in the IS label. (DTX-11.0013, Study 4).

c. The "Failed" Phase III Studies

558. PSY-3002 was a Phase III study to test whether "paliperidone palmitate is not clinically less effective that Risperdal Consta" for treating schizophrenia, (PTX-283 at 20, but paliperidone palmitate was not shown to be non-inferior. (*Id.* at 324; Gopal Tr. 1087:7–13, 1219:1–3; Verm. Tr. 780:15–781:1, 887:11–13).

559. PSY-3003 was another Phase III study to test fixed doses of 50, 100, and 150 mg-eq. paliperidone palmitate in the gluteal on Days 1, 8, 36, and 64. (PTX-286 at 22; Gopal Tr. 1051:17–23; *see also* Verm. Tr. 780:10–14).

560. The results of PSY-3003 showed that 100 mg-eq. injections were "statistically significantly better than placebo" in reducing PANSS scores, (Verm. Tr. 893:15–17; Gopal Tr. 1147:3–9, 1061:21–24; PTX-286 at 266), but the other doses did not reach

statistical significance. (PTX-286 at 266).

561. During the PSY-3003 trial, a "medication kit allocation error" caused subjects who were supposed to receive 150 mg-eq. doses to be mixed with placebo, and vice versa. (PTX-286 at 35–36; Gopal Tr. 1063:24–1064:8, 1168:22–1169:11, 1169:22–25; Verm. Tr. 894:1–3, 6–17). As a result, only 30 subjects received all intended doses of 150 mg eq. (PTX-284 at 37, Table 2; Gopal Tr. 1063:24–1064:12).

562. The medication kit allocation error "had nothing to do with the 150-milligram dose regimen itself. It was just an error in the way the study was conducted[.]" (Verm. Tr. 895:1–7).

563. PSY-3004 was another Phase III study to test doses of 25, 50, and 100 mg-eq. paliperidone palmitate in the gluteal on Days 1, 8, 36, and 65. (PTX-284 at 21, 23; Verm. Tr. 779:25–780:9; Gopal Tr. 1050:24–1051:11).

564. The results of PSY-3004 showed that all three dose amounts were effective and provided a "statistically significant improvement in total PANSS score." (PTX-284 at 240; Gopal Tr. 1055:15–25).

565. Although Dr. Gopal considers all three studies—PSY-3002, PSY-3003, and PSY-3004—"failures" and "disasters," (Gopal Tr. 1055:16–17, 1066:1–5, 1087:7-14), his testimony lacks credibility.

566. Dr. Gopal was not involved with the design or testing of PSY-3002, PSY-3003, or PSY-3004, was subject to a "firewall" from the project at the time, and his

testimony is based entirely on observing meetings through a window next to the coffee machine. (Gopal Tr. 1056:6–1057:4).

567. Moreover, PSY-3003 and 3004 were included on Janssen's label for IS, and described each study's particular successes. (DTX-11.0013 (Studies 2, 3); Gopal Tr. 1130:17–20, 1133:17–19).

568. Indeed, Janssen's "advisors were very positive about the results of the Phase I, II, and III data, and the overall regulatory probability of success for paliperidone palmitate," (PTX-92 at 1; Verm. Tr. 908:22–909:2), and thought the data from PSY-3003, and 3004 "would be more than adequate to support an indication [of] schizophrenia" for Janssen's paliperidone palmitate product. (Verm. Tr. 909:21–25).

d. The "Successful" Phase III Studies

569. PSY-3006 was a "backup" Phase III to re-do the PSY-3002 study and "demonstrate that paliperidone palmitate is not less effective than Risperdal Consta" with a different dosing regimen. (PTX-371 at 23; Verm. Tr. 820:6–22).

570. Rather than the 50 mg-eq. dose used in PSY-3002, PSY-3006 required a 150 mg-eq. dose in the deltoid on Day 1. (Verm. Tr. 821:4–7; 821:25–822:3).

571. Additionally, on July 24, 2007, Janssen amended the study protocol to replace the 50 mg-eq. Day 8 injection with a 100 mg eq. into the deltoid, (PTX-371 at 26; PTX-258 at 2; Verm. Tr. 823:20–824:9; Gopal Tr. 1217:6–8), but some patients still received 50 mg-eq. on Day 8. (PTX-371 at 89).

572. At the time of the amendment, there was not "any safety concern with paliperidone palmitate or that the risk benefit profile of paliperidone palmitate didn't remain positive." (Gopal Tr. 1221:9–16; PTX-256 at 1).

573. The results of PSY-3006 demonstrated "that paliperidone palmitate had comparable efficacy to Risperdal Consta[.]" (PTX-371 at 172).

574. The individual PK data for PSY-3006 also showed that many of the subjects who received 150/50 mg-eq. doses on Days 1 and 8 reported plasma concentrations above the 7.5 ng/mL therapeutic threshold by Day 8, and stayed within a therapeutic window substantially between 7.5–40 ng/mL for the entirety of the study. (*See* PTX-371 at 3221–3361 (JANUS00969848–988)).

575. PSY-3006 thus showed that a loading dose regimen of 150/50 mg-eq. in the deltoid on Days 1 and 8 would be sufficient for many patients. (FF 574).

576. PSY-3007 was another "backup" Phase III study to test a dosing regimen of 150 mg-eq. in the deltoid on day 1, followed by 25, 100, or 150 mg-eq. in the deltoid or gluteal, "at the discretion of the investigator." (PTX-351 at 21; Gopal Tr. 1179:12–1180:3).

577. PSY-3007 showed that all three regimens—150/25 mg-eq., 10/100 mg-eq., and 150/150 mg-eq. on Days 1 and 8, respectively—"gave statistically significant results over placebo," (Gopal Tr. 1181:23-25, 1181:1-6; PTX-351 at 185), as described in the IS Label (DTX_11.0013 (Study 1)), with subjects in the 25 and 150

mg-eq. arm showing efficacy by Day 8 (Gopal Tr. 1182:13–15; PTX-351 at 105).

578. The clinical studies collectively tested several different paliperidone palmitate formulations with a range of different particle sizes. (PTX-441 at 11, Table 1; PTX-278a at 147; PTX-381 at 1; PTX-382 at 1; PTX-165 at 1).

2. Other Doses, Dosing Regimens, and Injection Sites Work

579. "The optimal regimen is a subjective determination based on how you want to balance the number of patients getting into the efficacious window or therapeutic window and not pushing them over the top into an adverse event risk." (Gopal Tr. 1228:13–19).

a. The Amount of Each Loading Dose Is Not Critical

580. The only difference between the administration of different amounts of paliperidone palmitate as loading doses is the percentage of patients who reach the therapeutic window, which is a difference in degree, not in kind, and thus the amount of each loading dose is not critical.

581. As of August 14, 2007, Janssen had been considering two different "preferred dosing regimens" with different loading dose amounts:

> (1) "Day 1 and day 8 of 100 mg eq. deltoid injections followed by" monthly gluteal injections of 25, 50, or 100 mg-eq.; and
>
> (2) "Day 1 and day 8 of 150 and 100 mg eq. deltoid injections followed by" monthly gluteal injections of 25, 50, or 100 mg-eq.

(PTX-278A at 35–36; Samtani Tr. 1358:12–1359:5).

582. The 150/100 loading dose regimen was intended "to match the 90 percent

level [of patients reaching the therapeutic threshold] of the oral [Invega ER]." (Samtani Tr. 1428:23–25).

583. The development team analyzed loading dose regimens of "75/75 versus 100/100 versus 150/100," (Samtani Tr. 1375:17–19, 1375:24–1376:16), and predicted the median patient would reach the therapeutic window and stay there, but also that some patients would either not reach the therapeutic window, or exceed it, regardless of the loading dose regimen used, (*id*. 1425:23–1426:1; PTX-788a at 4).

584. The only difference between the three loading dose amounts is the percentage of patients that reach the therapeutic window by Day 8. (*See* FF 98; Gopal Tr. 1203:6–17, 1204:16–23, 1205:17–24; Samtani Tr. 1378:14–1379:11; *see also* PTX-348a, slide 5; PTX-788a, slide 5).

585. Janssen was also willing to launch IS with a 100/100 mg-eq. loading dose regimen "[i]f the backup studies failed," showing a 150/100 mg-eq. loading dose regimen is not critical. (Gopal Tr. 1167:6–12; FF 93–94).

b. The Administration of a Second Loading Dose Is Not Critical

586. The only difference between dosing regimens with and without a second loading dose is the percentage of patients who remain at therapeutic plasma concentrations until the maintenance dose (or second monthly dose), which is a difference in degree, not in kind. (FF 548, 587).

587. A second loading dose on Day 8 does not contribute to rapid efficacy for

"patients to get into the therapeutic window within a week," (Samtani Tr. 1361:20–1362:18; Kahn Tr. 2306:25–2308:2; PTX-278A at 118, 119).

c. Injection Site is Not Critical

588. The only difference between administering injections in the deltoid and gluteal muscles is the percentage of patients who reach the therapeutic threshold, which a difference in degree, not in kind, (FF 589–591; Samtani Tr. 1431:21–1432:1, 1435:24–1436:2, 1436:11–14), and thus the injection site is not critical.

589. Janssen represented to the FDA that "[w]ith initiation doses of 25, 50, 100, or 150 mg eq. on Day l in the deltoid muscle 20%, 49%, 73%, and 84% of subjects, respectively, would achieve the paliperidone concentration threshold value of 7.5 ng/mL at 1 week after initiating treatment. Similarly, for gluteal injections, the corresponding percentages would be 8%, 26%, 52%, and 66%." (PTX-370 at 85).

590. Even accounting for differences in BMIs, Janssen predicted that administering the same amount into the deltoid of normal, overweight, obese, and morbidly obese patients would result in 78.3, 71.4, 71.0, and 57.7% of patients reaching the therapeutic threshold by Day 8, compared to 63.7, 51.7, 39.3, and 21.6%, respectively, for gluteal injections. (PTX-294A at 43 (slide 43); Samtani Tr. 1430:3–7, 1433:15–24).

591. Even using longer needles to inject 150/100 mg-eq. loading dose into the deltoid, 17% of subjects that are overweight, 16% of patients that are obese, and

33% of patients that are morbidly obese would still fail to reach the therapeutic threshold of 7.5 ng/mL. (Samtani Tr. 1380:10–1381:2; PTX-370 at 49).

3. The Expected BMI Effect

592. The "BMI effect" that arose in Janssen's clinical studies was not unexpected.

593. Selecting the deltoid for the loading doses was a business decision to minimize development costs, and did not lead to unexpected results.

594. One reason this "BMI effect" first appeared in PSY-3002, 3003, and 3004 is because they were the first studies that eliminated a BMI cap excluding morbidly obese patients from the earlier paliperidone palmitate studies. (*Compare* PTX-279 at 27, 68; PTX-181 at 24, 49; PTX-269 at 18, 42; PTX-674 at 23, 53; (SCH-201, USA-3, PSY-1001, PSY-1004 all having BMI "Inclusion Criteria" somewhere between 15–35 kg/m^2 and subjects ranging from 16–41 kg/m^2), *with* PTX-283 at 26, 77; PTX-286 at 27, 75; PTX-284 at 27, 71 (PSY-3002, PSY-3003, PSY-3004 all having BMI minimums of 15 or 17 kg/m^2 and no upper limit, and subjects between 16–68.9 kg/m^2); Gopal Tr. 1140:10–16, 1143:18–20, 1144:5–12, 1219:6–9, 1220:2–4; Verm. Tr. 864:11–14, 865:3–5, 891:5–7, 982:2–4, 982:9–11).

595. PSY-3006 had an "Inclusion Criteria" that set only a minimum BMI of "17 kg/m^2." (PTX-371 at 28), yet the BMI of all subjects remained low from 17–41 kg/m^2. (PTX-371 at 70; Gopal Tr. 1218:18–22).

596. Janssen knew their paliperidone palmitate injections struggled in high BMI

patients, so they elected to cap the BMI of subjects in PSY-3007 at 40 kg/m^2 to ensure it would be a success. (DTX-351 at 28; Gopal Tr. 1178:20–1179:1).

597. But a POSA would have known that "[p]eople with high BMI . . . have more adipose [(or fat)] tissue than people with normal BMI." (Gopal Tr. 1156:21–23).

598. As early as March 23, 2005, Janssen knew that "the difference in thickness of subcutaneous fat between arm and buttock" caused lower paliperidone plasma levels and "[t]he hypovascularity of subcutaneous adipose" caused slower absorption for injections in to the gluteal. (PTX-181 at 84; *see also* DTX-536 at 21; Gopal Tr. 1156:2–17, 1165:12–19).

599. In fact, Janssen represented to the FDA that "[p]ublications suggested that [] approximately one-third of injections given at the gluteal site are not administered properly into the muscle [ ] due to the relatively high concentration of adipose tissue at this site." (PTX-370 at 65; Samtani Tr. 1452:5–14).

600. A POSA would have known generally that "an intramuscular injection has to be injected into the muscle." (Sinko Tr. 2088:20–23).

601. A POSA would have also known that "at the deltoid injection site, the likelihood of an injection that is truly int[ra]muscular is higher compared to the gluteal injection site." (PTX-370 at 47; Samtani Tr. 1451:11–15).

602. Janssen decided early in development to use only 1.5" needles for the gluteal. (*See* PTX-278a at 148) (showing all clinical studies used 1.5" gluteal needle).

603. But Janssen knew as of March 23, 2005, that "the mean gluteal-fat thickness (5.0 cm) exceeds the length of the needle (3.8 cm)." (PTX-181 at 84).

604. PSY-3002 showed "paliperidone palmitate was, in fact, noninferior to Risperdal Consta" for "subjects with normal weight". (Verm. Tr. 891:22–25; PTX-283 at 108, Fig. 9). "So really the problem in [PSY-3002] . . . was in the obese patients." (Verm. Tr. 892:22–25, 889:1–4, 9–23; Gopal Tr. 1220:16–22).

605. In PSY-3002, "the paliperidone palmitate needle was [1.5] inches, and the Ripserdal Consta syringe needle was 2 inches." (Verm. Tr. 900:13–16).

606. "Janssen could have used a 2-inch needle in the gluteal," for paliperidone palmitate, (Verm. Tr. 900:21–23), but it lacked any data for that needle length, (Verm. Tr. 903:20–22), and therefore it would be a "nightmare," requiring "starting technical development all over again." (Verm. Tr. 902:3–5; PTX-215 at 2; *see also* Samtani Tr. 1437:6–10, 1437:14–16).

607. Instead of making the gluteal needle longer, Janssen switched the loading dose injection site to the deltoid and increased the dose. (Verm. Tr. 902:10–13, 903:11–18; Samtani Tr. 1371:9–13, 1450:11–16; *see also* PTX-370 at 47).

608. Janssen sought to ensure that it quashed the BMI effect by providing two different needles for the deltoid—1" and 1.5", (Verm. Tr. 902:10–13, 903:11–18; Samtani Tr. 1371:9–13), but only because it already had data for both of those needles from prior studies. (FF 602).

609. Deltoid injections are not critical to the claimed dosing regimen, since a 2" gluteal needle would have likely provided the substantially the same results.

G. No Skepticism

610. There is no record evidence of skepticism of the claimed dosing regimen.

611. Dr. Kohler's anecdotal testimony regarding his and "colleagues" concerns about the dose amount for the first two loading doses merits little weight, (Kohler Tr. 1907:7–1908:21), as Dr. Kahn has not heard of similar concerns, and has "not seen any papers published to that effect." (Kahn Tr. 2322:24–2323:5).

612. The FDA's recommendation that Janssen's label include a loading dose regimen of "75–100" mg-eq. is not evidence of skepticism; "[t]hat's just giving advice to explore a lower dose." (Kahn Tr. 2364:8–2365:2; FF 95–96).

613. Lieberman "focuses on patients who have never been exposed to antipsychotics" and would not "be eligible for treating with long-acting injectables." (Kahn Tr. 2376:15–2377:23; *see* PTX-808).

614. "[O]lanzapine and aripiprazole[] are actually very often given at the highest dose in the label . . . as the initial treatment in schizophrenia patients." (Kahn Tr. 2379:4–2380:2).

H. No Industry Praise

615. There is no record evidence of industry praise for the claimed dosing regimen.

616. Dr. Gopal did not present any documentary support for IS's nomination for

the Prix Galien Award, and testified only that he "think[s]" it made it to "the finals, but it didn't win the award," and Janssen may have nominated itself. (Gopal Tr. 1046:12–1047:3, 1240:20–1241:3).

617. A slide deck created by an FDA employee discussing Janssen's modeling work with paliperidone palmitate is not probative of non-obviousness of the claimed dosing regimen, (PTX-431 at 1; Samtani Tr. 1393:3–13), as the '906 Patent does not claim a new method of modeling. (*See generally* DTX-1/PTX-1 at cls. 1–21).

618. Einarson does not solely analyze the claimed dosing regimen; it aggregated data from multiple studies, including studies that used unclaimed regimens. (Kohler Tr. 1994:22–1995:2; PTX-134 at 3, Table 1 (citing "Average of Gopal et al." at n.18); DTX-184 at 1 (citing NCT00147173 as the source); DTX-55/PTX-54).

619. NCT00210548 and NCT00147173 are "duplicates" of one another; they are the same study with two different reference numbers. (DTX-55/PTX-54 at 1).

620. Einarson is "not a trial," "it's a study in the Czech Republic" that looked "at the cost of three long-acting antipsychotics." (Kahn Tr. 2323:17–2324:17).

621. While Einarson concluded that IS costs less for the Czech Republic, that cannot be extrapolated to the U.S. because of differences in costs between the two healthcare systems. (Kahn Tr. 2325:3–25, 2415:9–2416:25).

622. Einarson reported the "QALYs" (or change in years of healthy life) was 0.817 for IS, 0.811 for olanzapine intramuscular, and 0.809 for Risperdal Consta, (PTX-

134 at 4, Table 4), which equates to 2–3 of extra healthy life using IS, which is "not a material difference." (Kahn Tr. 2324:18–2325:2, 2325:3–25).

623. Emsley is merely a review of "all the studies that used paliperidone palmitate in schizophrenia at that point in time," and does not independently examine the claimed dosing regimen. (Kahn Tr. 2442:9–17; PTX-133).

624. Emsley also discusses the pitfalls of Invega Sustenna: that "[t]here was no statistically significant difference in the rate of efficacy failure for [paliperidone palmitate (PP)] compared with haloperidol decanoate," and further noted that IS led to had metabolic side effects and led to increased healthcare costs. (PTX-133 at 9 (page 213); Kahn Tr. 2412:9-23, 2443:8-2444:4).

625. Emsley received research funding from Janssen. (PTX-133 at 17 (p. 221)).

626. The Lawrence & Taylor supplements are a collection of articles commissioned by Janssen, (PTX-506 at 7–8), so that "sales reps [can] give it out," (Kahn Tr. 2441:7–19, 2424:8–2425:5), and is not probative of industry praise.

XII. INDEFINITENESS

A. Indefiniteness of "Average Particle Size (d50)"

627. Particle size is typically described as part of a distribution, such as d10, d50 and d90. These values mean that 10, 50, or 90% of the particles, respectively, are below the reported size. (Block Tr. 587:20–588:4).

628. The '906 Patent specification uses the term d50 in the context of "an effective

average particle size (d50) of less than 2,000 nm means that ***at least*** 50% of the particles have a diameter of less than 2,000 nm . . . .” (DTX-1/PTX-1 at 7:32–35; Block Tr. 586:13–19) (emphasis added).

629. A POSA would not know what constitutes a “d50 of from about 1600 nanometers to about 900 nanometers” in claims 20 and 21 of the ’906 Patent, (Block Tr. 581:2–5, 8–12), because there are multiple ways to measure a d50 value, each of which may produce different results, (*id*. at 596:9–14).

630. The paliperidone palmitate particles described in the ’906 Patent are “irregular,” “not symmetrical.” (Block Tr. 591:12–17; *see also* DTX-121.0005).

631. A POSA would know that the particle size of irregular particles is measured by “an equivalent spherical diameter” where “[y]ou are making measurements of the diameter of a particle as if it were a sphere.” (Block Tr. 593:20–23).

632. In order to create an “equivalent sphere” from irregular-shaped particles, a POSA would know that numerous different “d-values,” including $\mathbf{d_{max}}$, $\mathbf{d_{min}}$, $\mathbf{d_w}$, $\mathbf{d_v}$, $\mathbf{d_s}$, $\mathbf{d_{seive}}$, or $\mathbf{d_{sed}}$, may be used to define the equivalent sphere’s diameter, (DTX-114.0005; DDX4-18), each of which uses a different characteristic of the particle to generate the diameter of the “equivalent sphere,” which can produce different results. (Block Tr. 594:20–596:4; *see* Sinko Tr. 2194:14–16).

633. The ’906 Patent specification does not mention which of $\mathbf{d_{max}}$, $\mathbf{d_{min}}$, $\mathbf{d_w}$, $\mathbf{d_v}$, $\mathbf{d_s}$, $\mathbf{d_{seive}}$, or $\mathbf{d_{sed}}$ to use when measuring particle size. (*See generally* DTX-1/PTX-1).

634. Particle size distributions can also be reported numerous ways, such as: (1) a "number-based distribution," meaning there are an equal "number of particles" both below and above the d50 value; or (2) "a volume-based distribution," meaning "half the [total] volume [is] taken up by particles" both below and above the d50 value. (Block Tr. 598:13–25, 599:5–11). Particle size can also be reported as intensity or weight distributions as well. (*Id*. at 599:19–22).

635. A POSA would not expect the d50 values of a number-based and volume-based distribution to be the same, (Block Tr. 599:12–14, 603:25–603:4; *see also* Sinko Tr. 2190; DTX-115.0001 (different techniques produce "different values for the mean particle size and the overall distribution"); DDX4-21).

636. A POSA would not know what type of distribution "dl50" to which Example 1 of the '906 Patent refers. (Block Tr. 587:8–17; DTX-1/PTX-1 at Table 1).

637. A POSA would "infer" the '906 Patent describes a "number-based distribution," not a "volume-based distribution," based on the language used. (Block Tr. 612:2–14; FF 628).

638. A POSA would also know there are numerous techniques and machines with which particle size could be measured. (*See, e.g.*, Block Tr. 589:4–13, 590:9–13; DTX-129.0004–0005).

639. The '906 Patent allows measurement by any "art-known conventional techniques," such as "sedimentation field flow fractionation, photon correlation

spectroscopy and disk centrifugation," as well as "laser defraction [*sic*] analysis." (Block Tr. 589:4–7, 11–13, 590:7–8; DTX-1/PTX-1 at 7:37–39). A POSA would have also known of other "art-known conventional techniques" in addition to those described. (Block Tr. 591:5–7; Sinko Tr. 1553:24–1554:3; DTX-117.0157; Block Tr. 596:25–597:8; *see also* DDX-4.20).

640. While each technique use "the concept of an equivalent spherical diameter," they "do not" "use the same aspect or characteristic[]" d-value. (Block Tr. 597:13–19). For instance, "[a] cyclone device would be influenced by the weight of the particle," whereas a "coulter counter could be measuring the volume of a sphere." (Block Tr. 597:20–598:4). In other words, "the equivalent particle diameter is defined not only by the physical particle attribute measured, . . . but also by the measurement technique." (DTX-128.0007).

641. A POSA would not always measure particle size of paliperidone palmitate by laser diffraction. (Block Tr. 611:7–15).

642. A "report of a conference that was co-sponsored by the Food and Drug Administration and by the United States Pharmacopeia" notes that "[t]he same sample analyzed on different instruments more often than not produces different results." (DTX-116.0008; *see also* Block Tr. 607:5–21).

643. REDACTED

REDACTED

REDACTED

644. REDACTED

REDACTED

REDACTED

645. A POSA would not employ "orthogonal techniques"—or different measurements—to validate the particle size "[b]ecause one ordinarily does not employ orthogonal techniques. . . [and] the patent doesn't specify a procedure for validation of the outcome of these measurements." (Block Tr. 612:24–613:12).

646.

648. The '906 Patent does not inform a POSA "what instrument to use," "the experimental conditions," or "how to prepare the sample." (Block Tr. 679:6–21).

649. Although Dr. Sinko opined the claimed d50 range is definite because a POSA could "prepare samples and put them in the machines and press the right buttons and

get the results out," (Sinko Tr. 1553:6–16), Dr. Sinko failed to explain how a POSA would choose the type of d-value, particle size distribution, method of analysis, machine, and/or sample preparation protocol to reliably test the claims.

650. Dr. Sinko's own textbook confirms the ambiguity surrounding particle size measurements, as well as the various ways by which it can be measured. (*See* DTX-73.0527 (use of "an equivalent spherical diameter"); DTX-73.0530-34 (describing number and weight distributions with different results (Fig. 19-2, 19-4)); DTX-73.0535 ("Many methods are available for determining particle size.").

B. Indefiniteness of "Nanoparticle Suspension"

651. The term "aqueous nanoparticle suspension" does not have a typical meaning in the art. (Block Tr. 614:17–20).

652. The '906 Patent specification does not explain what size particles fall within the term "aqueous nanoparticle suspension." (Block Tr. 614:23–25).

653. The statement that, preferably, "the nano particles would [have] an averages [*sic*] size of less than 2000 nm to about 100 nm," (DTX-1/PTX-1 at 7:24–27) "doesn't define a nanoparticle suspension." (Block Tr. 615:11–15) "There could be smaller or larger particles than those described[.]" (Block Tr. 615:16–22).

654. The '843 Patent, which is incorporated by reference in the same paragraph as the preferred particle sizes, describes formulations with particles exceeding 15,000 nm in size (or 15 micrometers). (DTX-71.0005 at 7:61–64).

655. The ’544 Patent, which is also incorporated by reference as teaching “suitable” formulations, defines nanoparticles as particles having an “effective average particle size [of] less than about 400 nm,” (DTX-54/PTX-55 at 2:31–36), but then describes a nanoparticle formulation with a preferred “effective average particle size” of less than “2,000 nm,” (*id*. at 5:16–26).

656. By incorporating by reference the ’843 Patent and ’544 Patent, the ’906 Patent effectively describes at least four different and contradictory particle sizes ranges, despite describing them all as suitable “nanoparticle formulations.”

657. “Based on the disclosure . . . in the specification,” a POSA could not “determine with reasonable certainty whether a formulation is a nanoparticle suspension within the meaning of Claims 10, 20, and 21. (Block Tr. 616:7–12).

XIII. WRITTEN DESCRIPTION

658. Neither claims 10 nor 13 require any particular level of renal impairment. (DTX-1/PTX-1 at cls. 10, 13; Kahn Tr. 119:14–16; Samtani Tr. 1439:4–5, 18–24; Kohler Tr. 1998:22–25).

659. Claims 10, 13, 20 and 21 cover dosing regimens for patients with mild, moderate, or severe renal impairment. (DTX-1/PTX-1 at cls. 8, 10, 11, 13, 20, 21).

660. The ’906 Patent specification contains only two passages related to renal impairment: (1) patients with renal impairment should be administered two loading doses of “about” 100/75 or 75/75 mg-eq., (DTX-1/PTX-1 at 3:27–56); and (2) for

patients "with ***mild*** renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses," (*id*. at 5:53–66; *see also* Kahn Tr. 115:8–11).

661. The '906 Patent specification does not describe an appropriate dosing regimen for patients with moderate or severe renal impairment, or when doses higher than 75 mg-eq. should be used. (*See generally* DTX-1/PTX-1; Kahn Tr. 134:8–17).

662. At most, the inventors created a dosing regimen using 100 mg-eq. as a loading dose for patients with *mild* renal impairment. (DTX-1/PTX-1 at 3:27–56, 5:53–66; Samtani Tr. 1438:8–10; 1438:18–23; FF 660–661).

663. The IS Label shows that the inventors did not invent a dosing regimen for moderate or severe renal impairment; the Label instructs not to administer paliperidone palmitate to such patients. (DTX-11.0001).

664. A POSA would know not to "treat a patient with mild renal impairment the same way as a person with severe renal impairment" because such a patient "the risk for accumulation is more severe." (Kahn Tr. 116:9–18).

665. A POSA would not "understand the inventors [of the '906 Patent] were in possession of a dosing regimen for administering paliperidone palmitate to a patient with any level of renal impairment." (Kahn Tr. 134:8–17).

666. Even if the term "from about 75 [mg-eq.]" has an implicit limit of 150 mg-eq., the inventors did not demonstrate possession of a 150 mg-eq. dose for patients with renal impairment. (Kahn Tr. 136:10–137:3; DTX-1/PTX-1 at 5:56–58).

XIV. CONCEPTION AND INVENTORSHIP

667. Dr. Vermeulen signed an oath that she and Alfons Wouters were the original and joint inventors of the '906 Patent on April 27, 2009. (Verm. Tr. 984:3–7; DTX-2/PTX-2 at 86-98).

668. According to Dr. Vermeulen, Alfons Wouters was "principally responsible" for the formulation development work. (Verm. Tr. 762:9–15).

669. Dr. Vermeulen testified that she contributed to "all of the clinical work" and "population PK analysis," and "propose[d] an alternative first dosing regimen, the 150 [mg-eq.] in particular." (Verm. Tr. 1020:23–1021:3). She also allegedly devised the "Day 1, Day 8" loading dose regimen. (Verm. Tr. 1023:5–9).

670. Janssen has not shown who *in toto* contributed to the conception of the claimed dosing regimen; it was a result of "teamwork" involving "tens of people" (Verm. Tr. 755:12–16, 1004:21–1005:5, 1005:18–21).

671. Dr. David Hough, Dr. Pilar Lim, Marielle Eerdekens, and Adrian Cleton all contributed to the IS project that resulted in the '906 Patent. (Gopal Tr. 1172:3–16; Verm. Tr. 1013:14–17, 1024:13–17). Additionally, Dr. Larry Ereshefsky was a "key opinion leader[]" assessing Janssen's clinical studies and helping refine the claimed loading dose regimen. (*See generally* DTX-409).

672. Neither Dr. Gopal nor Dr. Samtani corroborated their contribution to the conception of any aspect of the claimed invention. (Gopal Tr. 1175:22–1176:7;

1177:10–16; Samtani Tr. 1412:21–1413:1).

673. When Drs. Gopal and Samtani joined the development team in April 2006 and February 2007, respectively, Janssen had already settled on a formulation, (Samtani Tr. 1408:20–1409:4), dose amounts of 25–150 mg-eq., (*see* FF 208, 546–568) (exclusively using 25–150 mg-eq. doses after BEL-7), and loading doses on Days 1 and 8. (Verm. Tr. 767:6–768:6; PTX-165 at 1).

674. At most, Dr. Gopal testified that he "select[ed] the dosing regimen for the [PSY-3006 and -3007] trials," and "work[ed] closely with the modelers" to model different dose amounts or injection sites, (Gopal Tr. 1071:5–16), and in fact advocated against the claimed dosing regimen. (*Id*. at 1223:19–24; PTX-262).

675. By the time Dr. Samtani joined the team, "there was already a population pharmacokinetic model" created by Dr. Vermeulen. (Samtani Tr. 1411:5–10).

676. Although Dr. Samtani claims he found "a 25 percent dose reduction would be necessary for patients that have mild renal impairment," the claimed regimen does not reflect a 25 percent dose reduction, (Samtani Tr. 1389:4–16).

677. After the '918 Provisional had been filed, the team continued to debate whether a 150/100 or 100/100 loading dose regimen is most optimal. (Verm. Tr. 991:24–992:2; PTX-333 at 24).

678. The record evidence fails to demonstrate who contributed to the claimed range of days on which doses could be administered.

679. Each of Janssen's clinical study protocols gave doctors "some variability on the days" on which doses could be administered. (Gopal Tr. 1234:23–25).

680. Throughout most of Janssen's Phase II and Phase III trials, injections were not administered on the day prescribed by the protocols. (DTX-434.0043, Fig. 5; Gopal Tr. 1235:15–18, 1235:19–23, 1236:25–1237:6; Samtani Tr. 1443:25–1445:14; PTX-370 at 68–75 (showing Day 8 injections administered on Days 6-29; Day 36 injections administered on Days 15-57; Day 64 injections administered on Days 46-85).

681. Cristiana Gassmann-Mayer helped synthesize the data showing the range of days injections in the clinical study were administered. (Gopal Tr. 1238:19–25, 1240:7–10; PTX-252).

CONCLUSIONS OF LAW

I. PRIORITY & INVENTION DATE

1. The '906 Patent is not entitled to a priority date of December 19, 2007.

2. The '906 Patent is entitled to a priority date no earlier than December 5, 2008.

3. "[P]riority under § 120 is a legal determination based on underlying fact findings." *Natural Alternatives*, 904 F.3d at 1379.

4. The patentee bears the burden of proving that it is entitled to claim priority to the filing date of an earlier application. *See, e.g.*, *PowerOasis*, 522 F.3d at 1303–06.

5. "[A] patent's claims are not entitled to an earlier priority date merely because

the patentee claims priority." *In re NTP*, 654 F.3d at 1276.

6. "[T]o gain the benefit of the filing date of an earlier application . . . , each application in the chain leading back to the earlier application must comply with the written description requirement." *Zenon Environmental*, 506 F.3d at 1378.

7. If a priority document discloses a species of the claimed invention, the patentee must show that a POSA would have been able to "store[] in their minds" the full genus of the later-claimed invention. *In re Curtis*, 354 F.3d at 1356-57; *Regents of the University of California*, 119 F.3d at 1568.

8. The invention date is presumed to be the filing date "unless the inventor comes forward with evidence of an earlier invention date." *Mahurkar*, 79 F.3d at 1577; *Stamps.com*, 437 F. App'x at 907 (patentee bears the burden of invention date).

9. Courts have rejected the notion that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show." *In re Tanczyn*, 347 F.2d at 832. "[W]here the reference showed a species of the generic invention being claimed," that does not "authorize the overcoming of references by affidavits showing that the applicant had invented, prior to the reference date, a part, some parts, or even a combination of parts, used to create an embodiment of his claimed invention, where the part or parts are not within the scope of the claims being sought." *Id*. at 833 (distinguishing *In re Stempel*, 241 F.2d 755); *see In re Dardick*, 496 F.2d at 1240.

10. *In re Stryker*, did not change the law articulated in *Tanczyn*. Rather, the *Stryker* court merely found the applicant affidavit sufficient because the differences between the reference sought to be removed as prior art and the invention described in the affidavit were insignificant. 435 F.2d 1340.

II. INVALIDITY

A. The Asserted Claims Are Invalid as Obvious

11. Claims 2, 10, 13, 20, and 21 of the '906 Patent are invalid as obvious in view of the prior art, notwithstanding any evidence of secondary considerations.

12. Because each Asserted Claim is invalid, every claim of the '906 Patent is invalid. (D.I. 133 at 9) (identifying representative claims).

13. The presumption of patent validity is rebuttable. *Novo Nordisk*, 719 F.3d at 1352; 35 U.S.C. § 282.

14. Pre-AIA § 102 sets forth the seven enumerated conditions that preclude issuance of a patent. 35 U.S.C. § 102.

15. Pre-AIA § 103 sets forth a further condition that "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a); *KSR*, 550 U.S. at 406.

16. Obviousness is a question of law based on the underlying facts, in consideration of: (1) the level of ordinary skill in the art; (2) the scope and content

of the prior art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness. *KSR*, 550 U.S. at 406–07 (when a court "conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103") (citing *Graham*, 383 U.S. at 17–18).

17. A patentee may not "withdraw[] what already is known into the field of its monopoly and diminish[] the resources available to skillful men." *KSR*, 550 U.S. at 416. Prior knowledge provides "the threshold from which innovation" must be measured; "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *Id.* at 427.

18. "[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Technologies,* 224 F.3d at 1325.

19. The hypothetical POSA is presumed to know all of the teachings of the prior art references in the field of the invention. *See In re Nilssen*, 851 F.2d at 1403.

20. For obviousness, a POSA is "a person of ordinary creativity, not an automaton," and "in many cases a [POSA] will be able to fit the teachings of multiple patents together like pieces of a puzzle." *KSR*, 550 U.S. at 420-21.

21. The '556, '843, and '544 Patents "are presumed enabled" for all that they teach, including all "unclaimed (and claimed) material." *Amgen*, 314 F.3d at 1354-55, 1357; *see also Sebela*, 2017 WL 4782807, at *6 n.7.

22. Invalidating prior art need not disclose a level detail that is not disclosed or

claimed in the asserted patent itself. *Lockwood,* 107 F.3d at 1570.

23. Moreover, "[a]dmissions in the [asserted patent's] specification regarding the prior art are binding" for purposes of obviousness. *PharmaStem*, 491 F.3d at 1362.

24. Because the '556, '843, and '544 Patents, as well as WO '384, are "'incorporated by reference'" into the '906 Patent, they "[are] effectively part of the ['906 Patent] as if [ ] were explicitly contained therein." *Telemac*, 247 F.3d at 1329.

1. Selecting Particular Elements From General Teachings With Predictable Results Is Not Patentable

25. Combining "familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR,* 550 U.S. at 416.

26. Where "there are a finite number of identified, predictable solutions," "the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR*, 550 U.S. at 421; *see also Hoffmann-La Roche,* 748 F.3d at 1332.

27. Moreover, "the discovery of an optimum value of a variable in a known process is normally obvious." *In re Antonie*, 559 F.2d at 620; *Synvina*, 904 F.3d at 1006; *In re Aller*, 220 F.2d at 456; *In re Boesch*, 617 F.2d at 276.

28. The benchmark for "routine optimization" does not look to whether the inventors used "routine optimization," but rather whether a POSA would be able to "armed with the principles disclosed in the prior art." *Merck*, 874 F.3d at 730.

29. Where the art recognizes "a property is affected by the variable," the variable is "result-effective," the optimization of which is within the ordinary skill of the art.

In re Applied Materials, 692 F.3d at 1297; *see also Synvina*, 904 F.3d at 1010.

30. Here, it would have been within the skill of the art to optimize dose amounts of the prior art dosing regimens, and particle sizes of the prior art formulations, as both were recognized as result-effective variables.

31. "When 'about' is used as part of a numeric range," and "there is no narrowing claim construction . . . [t]he extension effected by 'about' must be tied to the purpose of the limitation in the claimed invention—not the purpose of the invention itself." *Par Pharmaceutical*, No. 20-1273, slip op. at 10-11 (Fed. Cir. Nov. 23, 2020).

32. A particle size of 740 nm is "about 900 nm" in the context of the '906 Patent.

33. The Asserted Claims of the '906 Patent are presumed obvious because each limitation is nothing more than a selection from known prior art options with predictable results. *See Synvina*, 904 F.3d at 1006.

34. "[W]hen a genus is so limited that a person of ordinary skill in the art can at once envisage each member of this limited class, a reference describing the genus anticipates every species within the genus." *Abbvie*, 764 F.3d at 1379; *see also Bristol–Myers*, 246 F.3d at 1380 ("[T]he disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited.").

35. Prior art directed to "intramuscular" injections anticipate injections into the deltoid, gluteal, or vastus lateralis muscles.

36. "[W]here there is a range disclosed in the prior art, and the claimed invention

falls within that range, there is a presumption of obviousness." *Tyco*, 642 F.3d at 1372–73; *Synvina*, 904 F.3d at 1001, 1006, 1011; *Galderma*, 737 F.3d at 734–38.

37. Where a range in the prior art overlaps or encompasses the claims, "[s]uch overlap itself provides sufficient motivation to optimize the ranges," *In re Applied Materials*, 692 F.3d at 1295, and "[a] *prima facie* case of obviousness typically exists," *In re Peterson*, 315 F.3d at 1330.

38. "In cases involving overlapping ranges, . . . even a slight overlap in range establishes a *prima facie* case of obviousness"; obviousness "is even more compelling" where the "claimed ranges are completely encompassed by the prior art." *In re Peterson*, 315 F.3d at 1329–30; *see also Galderma*, 737 F.3d at 737 (finding 0.3% adapalene obvious in view of prior art range of 0.01 to 1%); *Warner Chilcott*, 89 F. Supp. 3d at 673–74 (finding 100 mg of EDTA obvious in view of prior art range of 20–175 mg); *Ex parte Qinyun Peng*, 2018 WL 6338537, at *4 (finding claimed d50 obvious in view of prior art range).

39. The claimed first loading dose amount of 150 mg-eq. on Day 1 is presumed obvious in view of prior art that teaches doses of paliperidone palmitate ranging from 25–150 mg-eq., and/or first loading doses ranging from 50–150 mg-eq.

40. The claimed second loading dose amount of 100 mg-eq. on Day 8 is presumed obvious in view of prior art that teaches doses of paliperidone palmitate ranging from 25–150 mg-eq., and/or second loading doses ranging from 50–150 mg-eq.

41. The claimed maintenance doses of 25–150 mg-eq. in the deltoid or gluteal monthly are presumed obvious in view of prior art that teaches monthly doses of paliperidone palmitate ranging from 25–150 mg-eq. in the deltoid or gluteal.

42. The claimed d50 particle size range of 900-1600 nm is presumed obvious in view of prior art that teaches at least a d90 of less than 2,000 nm.

43. "[T]he existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious." *In re Peterson*, 315 F.3d at 1329–30. "[T]he patentee [must] come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma*, 737 F.3d at 737–38.

44. Janssen failed to meet its burden of production that the selections within the prior art range are non-obvious.

2. A POSA Would be Motivated to Combine the Prior Art

45. A claim is obvious if "a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention," and "would have had a reasonable expectation of success from doing so." *TWI Pharmaceutical*, 773 F.3d at 1193.

46. Motivation "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *DyStar*, 464

F.3d at 1361; *Allergan*, 726 F.3d at 1292; *see also Alza*, 464 F.3d at 1290 ("[T]he teaching, motivation, or suggestion may be implicit from the prior art as a whole[.]").

47. "[D]esign incentives and other market forces would prompt variations of" the prior art; "[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Peterson*, 315 F.3d at 1330.

48. Expert testimony is not a necessary prerequisite for a court to find a motivation to combine. *See Wyers*, 616 F.3d at 1239.

49. Where prior art refers to another prior art reference regarding the same subject matter, there is motivation to combine the two. *See Norian*, 363 F.3d at 1327–28.

50. Moreover, a POSA need not "be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval" *Bayer*, 874 F.3d at 1326.

3. A POSA Would Have a Reasonable Expectation of Success in Arriving at the Claimed Dosing Regimen

51. Where the prior art identifies variables ("dose size and injection frequency") and there are "only a limited number of permutations" from which to choose, a POSA would have a reasonable expectation of success in arriving at the claimed variable. *In re Copaxone*, 906 F.3d at 1025; *see also Pfizer*, 480 F.3d at 1366.

52. "Obviousness does not require absolute predictability of success," but rather only "a reasonable expectation of success." *See Medichem*, 437 F.3d at 1165.

53. A patent claim cannot escape obviousness "simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

54. The Federal Circuit "has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness,'" *Acorda*, 903 F.3d at 1333, because "[a]ll that is required is a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331; *see also Warner Chilcott*, 594 F. App'x at 635–36; *In re Montgomery,* 677 F.3d at 1380–1383 (finding Phase III protocol sufficient to anticipate a claim to a "method for the treatment or prevention of stroke or its recurrence"); *cf. OSI Pharmaceuticals*, 939 F.3d at 1385 (finding lack of reasonable expectation of success based on Phase II study without results only because 99.5% of similar Phase II trials failed).

55. As "safety[ ] and efficacy are not requirements of the asserted claims," Teva need not prove "'a reasonable expectation of success' with respect to . . . safety[or] efficacy." *Aventis Pharma*, 743 F. Supp. 2d at 342–43; *cf. Novartis*, 923 F.3d at 1054, 1060–62 (finding Phase I safety (not efficacy) data would not provide a reasonable expectation of success of a "therapeutically effective" amount of a drug).

56. Discussions of Phase III clinical trials, without associated data, may render obvious claims that do not require efficacy. *See Sanofi-Aventis*, 2018 WL 9364037, at *32–33, 35–36; *In re Montgomery*, 677 F.3d at 1375.

57. In ANDA cases, "[t]here is no requirement that one of ordinary skill have a

reasonable expectation of success in developing [the branded product]. Rather, the person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention." *Allergan*, 726 F.3d at 1292–93.

4. An Obvious Species Renders Obvious a Claimed Genus

58. "It is a long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo*, 793 F.3d at 1281.

59. An obvious species renders obvious the broader genus. *See Aventis Pharma*, 499 F.3d at 1300; *Ormco*, 498 F.3d at 1319; *In re Klein*, 987 F.2d at 1570.

60. Because the prior art renders obvious at least one dosing regimen that falls within the scope of the claims, the claimed dosing regimen is obvious.

5. Teva Has Established a Prima Facie Case of Obviousness

61. Teva has shown by clear and convincing evidence that each of the Asserted claims are *prima facie* obvious in view of the prior art.

62. No claim of the '906 Patent requires: (1) any level of safety or efficacy; (2) an optimal balance of safety and efficacy; (3) a dosing regimen that will work for a majority of patients; (4) efficacy in patients of any BMI; (5) the paliperidone palmitate formulation be unrefrigerated; (6) prohibiting the use of oral supplementation or oral tolerability; or (7) any particular level of renal impairment.

63. The claimed dosing regimen need be administered only to "a patient in need

of treatment," and thus only "requires a [POSA] 'treating' a patient to attempt to assist the patient." *Horizon Therapeutics*, 2015 WL 6165427, at *10; *see also Tyco*, 642 F.3d at 1374; *Aventis Pharma*, 743 F. Supp. 2d at 342–43.

64. Claim 2 is obvious in view of the '544 Patent and/or WO '384 in combination with the '548 Regimen, in view of Gibaldi, Goodman, Ereshefsky 1990, Ereshefsky 1993, Karagianis, Revill, and/or Janicak.

65. Claims 20 and 21 are obvious in view of the '544 Patent, WO'384, and '548 Regimen, in view of Gibaldi, Goodman, Ereshefsky 1990, Ereshefsky 1993, Karagianis, Revill, and/or Janicak.

66. Claims 10 and 13 are obvious in view of the '544 Patent, WO'384, and '548 Regimen, in view of Gibaldi, Goodman, Ereshefsky 1990, Ereshefsky 1993, Karagianis, Revill, Janicak, the '591 Application, Cleton 2007, and/or the 2006 Invega ER Label.

67. Claims 2, 10, 13, 20, and 21 are obvious in view of the '544 Patent, WO'384, the '548 Regimen, and/or Cleton 2008, in view of Gibaldi, Goodman, Ereshefsky 1990, Ereshefsky 1993, Karagianis, Revill, Janicak, the '591 Application, Cleton 2007, and/or the Invega ER Label (COL 64, 65, 66), respectively.

B. 3Janssen Has Failed to Provide Countervailing Evidence of Secondary Considerations

68. Janssen failed to meet its burden of production to provide evidence of secondary considerations of nonobviousness that would overcome Teva's strong

prima facie case of obviousness. *See Wyers*, 616 F.3d at 1245-46.

69. "A strong case of *prima facie* obviousness . . . cannot be overcome by a far weaker showing of objective indicia of nonobviousness." *Tokai*, 632 F.3d at 1371; *Western Union*, 626 F.3d at 1373.

1. No Nexus

70. For secondary considerations "to be accorded substantial weight, . . . a nexus must exist between the evidence and the merits of the claimed invention." *Torrent Pharmaceutical*, 853 F.3d at 1330; *In re Huai-Hung Kao*, 639 F.3d at 1068 ("Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus. . . ."); *Ohio Willow Wood*, 735 F.3d at 1344 (same); *AstraZeneca*, 88 F. Supp. 3d at 388–89; *see also Ethicon*, 812 F.3d at 1034 (finding nexus must be tied to novel features of combination of prior art elements, as opposed to unclaimed features or prior art feature in isolation).

71. "Evidence of secondary considerations must be reasonably commensurate with the scope of the claims." *In re Huai-Hung Kao*, 639 F.3d at 1068.

72. To be "entitled to a rebuttable presumption of nexus between the asserted evidence of secondary considerations and a patent claim," the patentee must show "that the asserted evidence is tied to a specific product and that the product *is* the invention disclosed and claimed." *Fox Factory*, 944 F.3d at 1373.

73. Where, as here, "a product embodies claims from two patents, a presumption

of nexus can be appropriate only if the claims of both patents generally ***cover the same invention***." *Id.* at 1377.

74. Claims 10 and 13 of the '906 Patent are not entitled to a presumption of nexus.

75. Because Janssen has alleged that IS embodies claims from multiple patents, none of the Asserted Claims are entitled to a presumption of nexus.

76. Absent a presumption, the patentee must "show[] that the evidence of secondary considerations is the direct result of the unique characteristics of the claimed invention." *Fox Factory*, 944 F.3d at 1373–74 (internal marks omitted).

77. Janssen's evidence of secondary considerations is afforded little weight, as it is attributable to prior art features, and not the novel aspects of the Asserted Claims.

2. Blocking Patents

78. Where "market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma*, 737 F.3d at 740; *see also Sanofi-Aventis*, 791 F. App'x at 928; *Acorda*, 903 F.3d at 1337; *Merck*, 395 F.3d at 1376–77; *Hofmann-La Roche*, 2012 WL 1637736, at *18 (finding commercial success of dosing regimen not probative in view of compound blocking patent).

79. Blocking patents render evidence of a long-felt but unmet need not probative of nonobviousness, which must be discounted. *See Acorda*, 903 F.3d at 1342.

80. Blocking patents "diminish[] possible rewards" for others and "reduc[e]

incentives for innovations in the blocked space." *Acorda*, 903 F.3d at 1339.

81. As of the priority date of the '906 Patent, the '952, '556, '843 and/or '544 Patents blocked competitors from commercializing paliperidone and paliperidone palmitate formulations, including for use in schizophrenia, which renders irrelevant any evidence of IS's commercial success and long-felt need.

82. A party cannot "play[] 'fast and loose' with the courts by prevailing twice on opposing theories." *Hallahan*, 744 F.3d at 510. "[A]bsent any good explanation, a party should not be allowed to gain an advantage by litigation on one theory, and then seek an inconsistent advantage by pursuing an incompatible theory." *In re Kane*, 628 F.3d at 638.

83. Teva's ability to conduct research in "blocked" space under § 271(e)(1)'s safe harbor provision does not eliminate the economic disincentives of potential liability if the product were commercialized. *See Acorda*, 903 F.3d at 1340–41.

84. A generic's pursuit of patents in a "blocked" space does not undermine the exclusionary force of any blocking patents, as "[i]t is elementary that a patent grants only the right to exclude others and confers no right on its holder to make, use, or sell." *Vaupel*, 944 F.2d at 879 n. 4; *Bio-Technology*, 80 F.3d at 1559.

3. Long-Felt Need

85. Janssen has not shown that, as of the priority date, there was a long-felt but unmet need for all of the benefits for which IS purportedly provides.

86. Janssen's evidence of a long-felt, unmet need lacks a nexus to the purportedly novel features of the claimed dosing regimen, and therefore is afforded little weight.

87. To show a long-felt, unmet need, Janssen must show an "articulated identified problem and evidence of efforts to solve that problem." *Texas Instruments*¸ 988 F.2d at 1178.

88. Janssen cannot merely point to drawbacks in the art; it must "show that these drawbacks constituted a long-felt, unmet need alleviated by the patent." *Perfect Web Technologies*, 587 F.3d at 1332; *see also Santarus*, 720 F. Supp. 2d at 455.

89. "[A]ttorney argument[] that the claimed invention meets [a long-felt] need" cannot supplant actual evidence establishing that the claimed invention met any alleged such need. *In re Karpf*, 758 F. App'x at 965.

90. For drug products, evidence of a "long-felt need" is of "limited value" where other treatment options were available before the filing date of the asserted patent. *Bristol-Myers Squibb*, 752 F.3d at 979; *AstraZeneca*, 88 F. Supp. 3d at 387–88.

91. Because drug products already existed in the prior art that met the field's purported needs, Janssen's evidence is of limited value and is afforded little weight.

4. Copying

92. There is no evidence of copying, beyond what was required as part of Teva's ANDA, that speaks to the nonobviousness of the claims.

93. Janssen's evidence of copying lacks a nexus to the purportedly novel features

of the claimed dosing regimen.

94. Federal regulations require that generic injectable drug products be both qualitatively (Q1) and quantitatively (Q2) the same as the reference drug with respect to both the active and inactive ingredients, meaning the generic must have the same ingredients (Q1) in the same amounts (Q2) as the reference drug. 21 C.F.R. § 314.94(a)(5)-(6), (a)(9)(iii).

95. Federal regulations also require generic drug products to be bioequivalent to the reference drug. 21 CFR § 320.21(b)(1).

96. Thus, "evidence of copying in the ANDA context is not probative of nonobviousness[.]" *Bayer*, 713 F.3d at 1377; *cf. Novartis*, 2009 WL 3754170, at *18; *Eli Lilly*, 2004 WL 1724632, at *38, n. 21 ("[T]he very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects.").

97. "[M]ore is needed than merely showing that similarity exists between the patent and the competitor's accused product." *Liqwd*, 941 F.3d at 1137.

98. Moreover, "[the copying] rationale is considerably weakened . . . by the fact that there are various other reasons why an invention may have been copied." *Aventis Pharma*, 2006 WL 2008962, at *45.

5. Failure of Others

99. While "[e]vidence that others tried but failed to develop the claimed invention," *In re Cyclobenzaprine*, 676 F.3d at 1081, or "to find a solution to the

problem which the patent[] in question purport[s] to solve," *Symbol Technologies*, 935 F.2d at 1578–79, may be relevant to obviousness, Janssen failed to present evidence demonstrating that anyone tried and failed to create a paliperidone palmitate dosing regimen or solve the problem IS purportedly solves.

100. Janssen's evidence of failure of others lacks a nexus to the purportedly novel features of the claimed dosing regimen.

101. When Courts look to the failure to get FDA approval, it is for a drug that serves as an ***alternative*** solution to the problem the patent addressed. *See Knoll Pharmaceutical*, 367 F.3d at 1385.

102. The relevance of a generic's regulatory difficulties to non-obviousness, generally, finds no support in the case law. *But see In re Cyclobenzaprine*, 2010 WL 3766530, at *1 (declining to follow the law of this District, finding only such evidence admissible under Federal Rule of Evidence 401).

103. Generally, relevant "failures" occur prior to public dissemination of the alleged invention. *See, e.g.*, *DePuy Spine*, 567 F.3d at 1328–29; *United Therapeutics*, 200 F. Supp. 3d at 279; *AstraZeneca*, 88 F. Supp. 3d at 390; *Eisai*, 247 F.R.D. at 443–44; *but see Allergan*, 2017 WL 1319555, at *4.

104. [redacted]

105. Failure of the inventors is irrelevant. *See AstraZeneca*, 88 F. Supp. 3d at 390.

6. Commercial Success

106. Because of the blocking patents (CL 81), Janssen's evidence of commercial success of IS is not probative of nonobviousness.

107. Janssen's evidence of commercial success lacks a nexus to the purportedly novel features of the claims, and is therefore not probative of nonobviousness.

108. "[A] court must be assured that the patentee's market domination is not attributable to monopoly power or other economic coercion, or to other factors unrelated to patent validity." *Graham*, 383 U.S. at 18, 36.

109. To show commercial success, Janssen must show "that the driving force behind the product sales was a direct result of the unique characteristics of the claimed inventions," rather than market forces such as pre-existing market share or marketing efforts. *WesternGeco*, 889 F.3d at 1330–31; *Pentec*, 776 F.2d at 316.

110. "If commercial success is due to an element in the prior art, no nexus exists." *Tokai*, 632 F.3d at 1369; *Ormco*, 463 F.3d at 1311–12.

111. Evidence of commercial success attributable to inherent properties of a drug product is weak evidence of non-obviousness of a claimed dosing regimen. *See Cubist Pharmaceutical.*, 75 F. Supp. 3d at 666–67.

7. Industry Praise

112. Janssen's evidence of industry praise is not probative of non-obviousness.

113. Janssen's evidence of industry praise lacks a nexus to the purportedly novel

features of the claimed dosing regimen.

114. To support a finding of nonobviousness, "[i]ndustry praise must . . . be linked to the patented invention." *Geo M. Martin*, 618 F.3d at 1305.

115. A nomination for an award, with no evidence tying the award to the novel features of the claim, is insufficient evidence of industry praise. *See South Alabama*, 808 F.3d at 827; *cf. Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1333 (Fed. Cir. 2019) (finding evidence of industry praise when the awards specifically commended the novel features of the claimed invention).

116. Likewise, "bare journal citations and self-referential commendation fall well short of demonstrating true industry praise. Furthermore, industry praise of what was clearly rendered obvious by published references is not a persuasive secondary consideration." *Bayer*, 713 F.3d at 1377. Indeed, articles sponsored by a patentee are given minimal, if any, weight. *See, e.g.*, *Amarin Pharma*, 449 F. Supp. 3d at 998.

8. Skepticism

117. Janssen's evidence of skepticism is not probative of non-obviousness.

118. "The focus of this consideration is skepticism of *others*, not skepticism of the inventors." *AstraZeneca*, 88 F. Supp. 3d at 383 (citation omitted).

119. "[L]ack of enthusiasm by a few" is not skepticism "such that the combination would not have been obvious to a" POSA. *BTG Int'l*, 923 F.3d at 1076.

120. All testimony related to the views, statements, or beliefs of "advisors" or

"colleagues" of Janssen's fact and expert witnesses is inadmissible hearsay if offered as evidence of skepticism. *See* Fed. R. Evid. 801-803; *Allergan*, 869 F. Supp. 3d at 490. At most, this testimony may be used only to show the witnesses' state of mind. *See Sotelo*, 707 F. App'x at 85.

121. Expert testimony of skepticism based on anecdotal evidence, without more, is insufficient to support nonobviousness. *See, e.g.*, *Bristol-Myers Squibb*, 923 F. Supp. 2d at 679–80; *Allergan*, 869 F. Supp. 2d at 490.

122. Statements from the FDA that "reflect[ ] attention to the FDA's normal duties ensuring the safety and efficacy of new drugs" does not rise to the level of skepticism that a claimed dosing regimen would work. *Bayer*, 713 F.3d at 1377.

9. Unexpected Results and Criticality

123. Janssen's evidence of unexpected results is not probative of nonobviousness.

124. Janssen's evidence of unexpected results lacks a nexus to the purportedly novel features of the claimed dosing regimen.

125. A patentee may overcome the presumption of obviousness by showing that the invention "produce[s] a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *In re Aller*, 220 F.2d at 456; *Galderma*, 737 F.3d at 739.

126. "A claimed range that demonstrates such unexpected results is referred to as a 'critical' range, and the patentee has the burden of proving criticality." *Synvina*,

904 F.3d at 1006; *see also Warner Chilcott*, 89 F. Supp. 3d at 655-56 ("Where the difference between the claimed invention and the prior art is some range or other variable within the claims, the patentee must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results.").

127. "[I]n order to properly evaluate whether a [] property was unexpected, the court should have considered what properties were expected." *Pfizer*, 480 F.3d at 1371. There can be no showing of unexpected results without evidence of what a POSA would have expected. *Id*.

128. "[T]he results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol*, 952 F.2d at 392; *see also Bristol-Myers Squibb*, 752 F.3d at 977; *Kao Corporation*, 441 F.3d at 970.

129. Indeed, proving criticality "requires more than a modest deviation from what was disclosed in the prior art." *Allergan*, 2017 WL 4803941, at *46; *Galderma*, 737 F.3d at 739 ("Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art.").

130. "Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time." *Galderma*, 737 F.3d at 739; *In re Budde*, 319 F.2d at 246 (ranges of reaction time and temperature constituted a difference in degree); *Aller*, 220 F.2d at 456–57 (improved yields, measured by percentages, reflect a

difference in degree); *In re Harris*, 409 F.3d at 1344 (32–43% increase in stress-rupture "does not represent 'difference in kind'" required for unexpected results).

131. Even "where an unexpected increase in efficacy is measured by a small percentage," if "the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind." *Galderma*, 737 F.3d at 739; *see also In re Aller*, 220 F.2d at 457, 459. Such evidence "does not rebut the strong showing" of the prior art. *Hoffmann*, 748 F.3d at 1334.

132. A claimed amount is not critical where the specification discloses that amounts outside the claimed amount were also effective. *See Warner Chilcott*, 89 F. Supp. 3d at 655–56; *see also In re Gardiner*, 171 F.2d at 316.

133. "[U]nsupported statements by the inventors, including in the specification, cannot support a finding of unexpected results." *Pernix*, 323 F. Supp. 3d at 617 n.15. Such testimony "is less compelling, coming as it does from persons with an interest in the validity of the patent." *Id.*

10. Teaching Away

134. Janssen's evidence of teaching away is not probative of non-obviousness.

135. Janssen's evidence of teaching away lacks a nexus to the purportedly novel features of the claimed dosing regimen.

136. A reference cannot be said to "teach away" from the claimed invention where "it merely expresses a general preference for an alternative invention but does not

criticize, discredit, or otherwise discourage investigation into the invention claimed." *Galderma*, 737 F.3d at 738; *see also SightSound*, 809 F.3d at 1320.

137. Failed studies are not *per se* evidence of teaching away. For instance, a "failure to generate statistically significant results points to a fault in the study," not that the claimed dosing interval was ineffective. *Hoffmann*, 748 F.3d at 1330.

C. Indefiniteness

138. Claims 20 and 21 are invalid under 35 U.S.C. § 112 for indefiniteness of the claimed "d50" range, as the '906 Patent fails to inform a POSA, with reasonable certainty, how to measure the "d50."

139. Claims 2, 20, and 21 are invalid under 35 U.S.C. § 112 for indefiniteness of the claimed "nanoparticle" term, as the '906 Patent fails to inform a POSA, with reasonable certainty, what constitutes a "nanoparticle."

140. "A patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus*, 572 U.S. at 901.

141. Indefiniteness is a question of law. *Sandoz*, 789 F.3d at 1341.

142. If a claim term is directed to a result or measurement, but the result or measurement can be arrived at multiple ways with different results, the claim term is invalid. *See Dow Chemical*, 803 F.3d at 634; *see also Sandoz*, 789 F.3d at 1341,

1344–45 (finding term "average molecular weight" indefinite because of numerous ways to measure particle size); *Otsuka*, 151 F. Supp. 3d at 546 (finding term "mean particle size" indefinite for same); *cf. Vapor Point*, 2013 WL 11275459, at *16-17 (finding term "micro-sized particles" sufficiently definite when the specification set forth express definition).

143. This is so regardless of whether someone skilled in the art could determine which method was the most appropriate. *See Dow Chem.*, 803 F.3d at 635.

144. Failing to inform a POSA how to prepare a sample for measurement may also render a claim term indefinite. *See Honeywell*, 341 F.3d at 1340.

D. Written Description

145. Claims 10, 13, 20 and 21 are invalid for failing to meet the written description requirement of 35 U.S.C. § 112, as a POSA would not understand the inventors to have possessed a dosing regimen for patients with any level of renal impairment, or administering doses in excess of 100 mg-eq. to such patients.

146. "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

147. The "level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Synthes*, 734 F.3d at 1341.

148. When an invention is described narrowly, the inventor cannot then claim broader unless the inventors showed that they recognizes the claimed features would apply broadly. *See Pernix*, 323 F. Supp. 3d at 619 (finding discovery that prior art formulation "did not require a dose adjustment" did not support the broader claim for a generic formulation); *Synthes*, 734 F.3d at 1342 (finding disclosure of "grooves," did not "constitute an adequate disclosure to claim all openings[.]"); *Eli Lilly*, 202 F. Supp. 3d at 994-97 (finding disclosure of 67% penetration enhancer provided insufficient written description for claimed 10-10,000%).

III. EXPERT OPINION TESTIMONY

149. "[A]n expert may express an opinion that is based on facts that the expert assumes, but does not know, to be true. It is then up to the party who calls the expert to introduce other evidence establishing the facts assumed by the expert." *Williams*, 567 U.S. at 57; *see also Micro Chemical*, 317 F.3d at 1394.

150. "Facts or data upon which expert opinions are based may, under the rule, be derived from three possible sources": (1) firsthand observation; (2) "presentation at trial" or (3) "presentation of data to the expert outside of court." Fed. R. Evid. 703, Advisory Notes; *see also Oracle*, 2011 WL 5914033, at *2; *Stecyk*, 295 F.3d at 414.

151. It is appropriate to discredit an expert's testimony where his "testimony proved, if nothing else, his lack of knowledge and familiarity" with the issues in the case. *Madden*, 873 F.3d at 974.

IV. INVENTORSHIP

152. "All inventors, even those who contribute to only one claim or one aspect of one claim of a patent, must be listed on that patent." *Vapor Point*, 832 F.3d at 1348–49. "A patent is invalid if more or less than the true inventors are named." *Trovan*, 299 F.3d at 1301; *see also* 35 U.S.C. §§ 101, 115, 116, 256, pre-AIA § 102(f).

153. Inventorship is a question of law. *General Electric*, 750 F.3d at 1329.

154. The named inventors are presumed to be correct. *See Hess*, 106 F.3d at 980.

155. "[A]n inventor can swear behind a reference by proving he conceived his invention before the effective filing date of the reference and was diligent in reducing his invention to practice after that date." *Apator*, 887 F.3d at 1295.

156. Because "[c]onception is the touchstone of inventorship," each joint inventor must contribute to conception of the invention. *Burroughs*, 40 F.3d at 1227–28.

157. Conception is "the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Burroughs Wellcome*, 40 F.3d at 1228. "[A] party must show possession of every feature" and "must have been known to the inventor at the time of the alleged conception." *James*, 823 F. App'x at 949 .

158. An idea is sufficiently "definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue" and "only ordinary skill would be

necessary to reduce the invention to practice, without extensive research or experimentation." *Burroughs Wellcome*, 40 F.3d at 1228.

159. "One who simply provides the inventor with well-known principles or explains the state of the art without ever having 'a firm and definite idea' of the claimed combination as a whole" is not a joint inventor. *Ethicon*, 135 F.3d at 1460.

160. To show co-inventorship, the alleged co-inventors must prove their contribution to the conception of the claims by clear and convincing evidence. *Ethicon*, 135 F.3d at 1461; *Hess*, 106 F.3d at 980.

161. "[A]n inventor's testimony . . . standing alone, [does not] rise to the level of clear and convincing proof." *Price*, 988 F.2d at 1194. "[T]he party must proffer evidence, in addition to [the inventor's] own statements and documents, corroborating the inventor's testimony." *Apator*, 887 F.3d at 1295. "Even the most credible inventor testimony is a fortiori required to be corroborated by independent evidence." *Medichem*, 437 F.3d at 1171-72.

162. Whether the inventor's testimony has been sufficiently corroborated is evaluated under a "rule of reason" analysis. *Price*, 988 F.2d at 1195. Under this analysis, "[a]n evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the [alleged] inventor's story may be reached." *Id*.

163. Janssen failed to provide any evidence corroborating at least Srihari Gopal and Mahesh Samtani's contributions to the conception of the claimed invention.

164. The record evidence fails to demonstrate that these purported inventors, but no other member of Janssen's paliperidone palmitate team, contributed to the conception of the claimed invention.

165. Janssen has failed to show that at least Srihari Gopal and Mahesh Samtani, are inventors of the '906 Patent.

V. JUDICIAL NOTICE

166. "The prosecution history is part of the intrinsic record of the patent and is a 'matter[ ] of public record. . . . It is thus subject to judicial notice." *Uniloc*, 772 F. App'x at 898 n.3; *see also Horizon Medicines*, 2019 WL 6907531, at *5 n.4 (same); *Eagle View*, 325 F.R.D. at 97 (same)

VI. REMEDIES

167. Teva is entitled to a judgment declaring the '906 Patent invalid for failure to comply with 35 U.S.C. §§ 103, and/or 112.

168. The case may be dismissed with prejudice.

169. Teva is entitled to a judgment awarding Teva its reasonable costs and attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285.

170. Teva is entitled to a judgment awarding Teva its costs.

171. Teva is entitled to a judgment awarding Teva all such other and further relief as this Court may deem just and proper.

Dated: December 11, 2020

Respectfully submitted,

s/ Liza M. Walsh
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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC. and JANSSEN PHARMACEUTICALS NV, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 2:18-00734 (CCC)(MF) **DECLARATION OF LIZA M. WALSH** *Filed Electronically*

I, Liza M. Walsh, do hereby declare as follows:

1. I am an attorney admitted to practice before this Court and a partner of the law firm of Walsh Pizzi O'Reilly Falanga LLP, counsel for Defendant Teva Pharmaceuticals USA, Inc. ("Teva") in connection with the above-captioned action.

2. I submit this Declaration in support of Teva's Post-Trial Brief and Proposed Findings of Fact and Conclusions of Law. I have personal knowledge of the facts set forth herein.

3. Attached hereto as Exhibit A is a true and correct copy of the prosecution history of U.S. Patent No. 5,254,556, which is a matter of public record accessible at <https://portal.uspto.gov/pair/PublicPair> by entering the patent number. The pages of document have been numbered and pertinent portions have been highlighted for the Court's convenience.

I hereby certify that the foregoing statements made by me are true. I am aware that if any of the foregoing statements made by me are willfully false, I am subject to punishment.

Dated: December 11, 2020

/s/Liza M. Walsh
Liza M. Walsh

Exhibit A

Practitioner's Docket No. JAB0828USDIV ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G. M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
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APPLICATION FOR INTERIM EXTENSION OF PATENT TERM (37 C.F.R. § 1.790)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. § 1.790, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for an interim extension of U.S. Patent No. 5,254,556 (the '556 Patent). In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Hal Brent Woodrow, represent that I am a registered patent practitioner signing on behalf of the patent owner.

B. RECORDAL OF ASSIGNMENT IN PTO

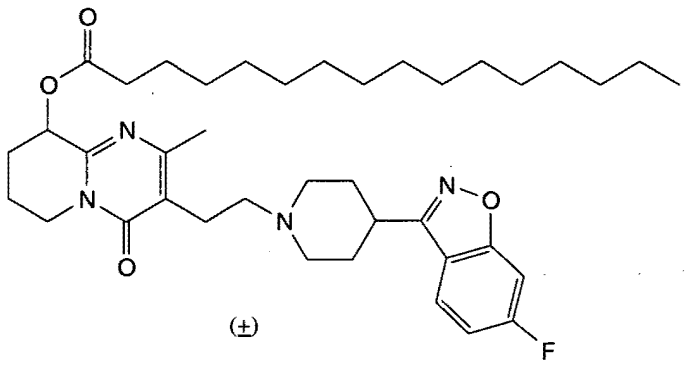
This application, U.S.S.N. 07/932,142, filed August 19, 1992, which is a Divisional of U.S.S.N. 07/422,847, filed October 17, 1989, now issued as US Patent No. 5,158,952, which is a Continuation-in-Part of U.S.S.N. 07/267,857, filed November 7, 1988, which was abandoned. An assignment of U.S.S.N. 07/422,847 was recorded: Date: November 13, 1989 at Reel/Frame: 05171/0567 847from the named inventors to Janssen Pharmaceutica, N.V., and an assignment of U.S.S.N. 07/422,847 was recorded: Date: October 4, 2006 at Reel/Frame: 018385/0112 from Janssen Pharmaceutica, N.V. to Janssen L.P; which was dissolved by the Limited Partner, Janssen , Inc., and General Partner Janssen Pharmaceutica Inc., when they merged and subsequently became Ortho-McNeil-Janssen Pharmaceuticals, Inc. were recorded in U.S.S.N. 07/422,847: Date: May 20, 2009 at Reel/Frame: 022708/0352 (copies of the merger documents are attached as Exhibit 1). Additionally to further clarify the record US Patent No. 5,254,556 was specifically assigned to Ortho-McNeil-Janssen Pharmaceuticals, Inc. on July 6th, 2009.

II. APPLICATION REQUIREMENTS (37 C.F.R. §§ 1.790 and 1.740)

A. IDENTIFICATION OF PRODUCT UNDERGOING REGULATORY REVIEW (1.740(a)(1))

The United States Food and Drug Administration ("FDA") is currently reviewing New Drug Application ("NDA") No. 22-264 for INVEGA SUSTENNA™ (paliperidone palmitate). The active ingredient of INVEGA SUSTENNA is paliperidone palmitate. The chemical name for paliperidone palmitate is [(9RS)-3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-9-yl] hexadecanoate, also known as C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Paliperidone palmitate has the following structural formula:



B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW IS CURRENTLY TAKING PLACE (1.740(a)(2))

Regulatory review for this product is currently occurring under the Federal Food Drug & Cosmetic Act, §505(b), 21 U.S.C. §355 (new drugs).

C. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

INVEGA SUSTENNA is a human drug product, the sole active ingredient of which is paliperidone palmitate. Neither paliperidone palmitate, nor any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

D. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of inventors: Cornelus G. M. Janssen
Alfonsus G. Knaeps
Ludo E. J. Kennis
Jan Vandenberk

Patent No.: 5,254,556

Date of issue: October 19, 1993

Expiration date: October 27, 2009

A copy of the patent, including the entire specification (with claims) and drawings is attached as Exhibit 2.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statement is attached as Exhibit 3.

A terminal disclaimer pursuant to 37 C.F.R. §1.321(a) was filed in the '556 Patent disclaiming the terminal part of the statutory term of any patent which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§154-156 and 173 of U.S. Patent No. 5,158,952. A copy of the disclaimer is attached as Exhibit 4. The '556 Patent remains commonly owned with U.S. Patent No. 5,158,952.

No certificate of correction or reexamination certificate has issued in the '556 Patent.

E. IDENTIFICATION OF CLAIMS READING ON THE PRODUCT SEEKING APPROVAL (1.740(a)(9))

The '556 Patent claims the active ingredient of the Product currently undergoing regulatory review which is paliperidone palmitate. The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

A claim chart that lists each applicable claim of the '556 Patent and demonstrates the manner in which each claim reads on the Product is attached as Exhibit 5.

H. STATEMENT THAT PATENT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

To the best of my knowledge, the '556 Patent meets all the eligibility criteria set forth in 37 CFR 1.710 and 1.720 for extension of patent term. It is not possible to determine the length of the extension that will ultimately be claimed since approval has not yet been granted for the product. Applicant expects the regulatory review period to extend past the expiration of the '556 patent, and is therefore requesting an interim extension for a period of one year, pursuant to 37 CFR 1.790(a).

I. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Hal Brent Woodrow, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein.

J. FEE (1.740(a)(14))

The Application fee due is $420.00 (37 C.F.R. § 1.740(a)(14) and § 1.20(j)(2).

Authorization is hereby made to charge the amount of $420.00 to Deposit Account No. 10-0750/JAB0828USDIV/HBW.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 10-0750/JAB0828USDIV/HBW.

K. CORRESPONDENCE

Please direct all inquiries and correspondence relating to this application to:

Philip S. Johnson, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

Attn: Hal B. Woodrow
Phone: (732) 524-2976
Facsimile: (732) 524-2808

L. COPIES (§ MPEP 2753 (8th Edition, Rev. No. 7).

Four additional copies of this application are attached, making a total of five copies being submitted.

Date: 6 July 2009

Hal Brent Woodrow

Hal Brent Woodrow
Registration No. 32,501
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
Tel. No. 732-524-2976
Customer No. 27777

Exhibit 5

Claims 1, 2 and 3 of U.S. Patent No. 5,254,556 Claim the Active Ingredient of the Product Seeking Approval or its Method of Use

1. A compound selected from the group consisting of a C_{2-20}alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, a pharmaceutically acceptable acid addition salt thereof, and an enantiomeric form thereof.	Paliperidone palmitate is a C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.
2. An antipsychotic composition comprising an inert carrier and as active ingredient an antipsychotic effective amount of the compound of claim 1.	The Product currently undergoing regulatory review comprises paliperidone palmitate, a C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, and one or more inert carriers provided in an amount sufficient to treat schizophrenia (a psychotic disorder).
3. A method of treating warm-blooded animals suffering from psychotic diseases, which method comprises the administration to said warm-blooded animals of an antipsychotic effective amount of the compound of claim 1.	The Product is currently undergoing regulatory review for the treatment of schizophrenia (a psychotic disease). The treatment comprises administering an antipsychotic effective amount of paliperidone palmitate, a C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Practitioner's Docket No. JAB0828USDIV ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G. M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR INTERIM EXTENSION

OF PATENT TERM (37 C.F.R. § 1.760)

Dear Sir:

Applicant hereby requests an Interim Patent Term Extension for a period of one (1) year as is provided under 35 U.S.C 156(e)(2) and 37 CFR 1.760.

BACKGROUND

An initial application for Interim Extension of Patent Term pursuant to 37 CFR 1.790 was filed on July 7, 2009 for US Patent 5,254,556 ('556 Patent). To applicant's knowledge the Interim Extension filed on July 7, 2009 has not been granted. The '556 Patent claims paliperidone palmitate, the active ingredient of the INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension (Product). The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

On July 31, 2009, the FDA granted a marketing authorization for the Product, which was under regulatory review under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

An Application for Patent Term Extension in compliance with 37 CFR 1.740 is being filed concurrently herewith.

The above-identified patent expires on October 27, 2009, less than three months from the date of this application for Interim Patent Term Extension.

FEE STATUS

Authorization is hereby made to charge the amount of $220.00 to Deposit Account No. 10-0750/JAB0828/HBW.

Practitioner's Docket No. JAB0828 ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G. M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

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APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. § 1.740, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for an extension of U.S. Patent No. 5,254,556 (the '556 Patent). In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Hal Brent Woodrow, represent that I am a registered practitioner appointed by the patent owner of record.

B. RECORDAL OF ASSIGNMENT IN PTO

This application, U.S.S.N. 07/932,142, filed August 19, 1992, which is a Divisional of U.S.S.N. 07/422,847, filed October 17, 1989, now issued as US Patent No. 5,158,952, which is a Continuation-in-Part of U.S.S.N. 07/267,857, filed November 7, 1988, which was abandoned. An assignment of U.S.S.N. 07/422,847 was recorded: Date: November 13, 1989 at Reel/Frame: 05171/0567 847 from the named inventors to Janssen Pharmaceutica, N.V., and an assignment of U.S.S.N. 07/422,847 was recorded: Date: October 4, 2006 at Reel/Frame: 018385/0112 from Janssen Pharmaceutica, N.V. to Janssen L.P; which was dissolved by the Limited Partner, Janssen , Inc., and General Partner Janssen Pharmaceutica Inc., when they merged and subsequently became Ortho-McNeil-Janssen Pharmaceuticals, Inc. were recorded in U.S.S.N. 07/422,847: Date: May 20, 2009 at Reel/Frame: 022708/0352 (copies of the merger documents are attached as **Exhibit 1**). Additionally, US Patent No. 5,254,556 was assigned by Janssen Pharmaceutica N.V. to Ortho-McNeil-Janssen Pharmaceuticals, Inc. on July 6th, 2009 at Reel/Frame: 022915/0992. Ortho-McNeil-Janssen Pharmaceuticals, Inc. is the marketing applicant for the approved Product.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

Four additional copies of this application are attached, making a total of five copies being submitted (See§ MPEP 2753 (8th Edition).

Date: 5 August 2009

Hal Brent Woodrow

Hal Brent Woodrow
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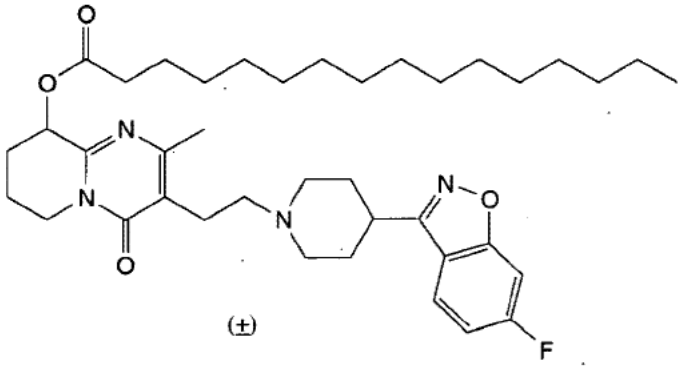
USA
732-524-2976
Customer No. 27777

II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") was approved in New Drug Application ("NDA") No. 22-264 for INVEGA SUSTENNA™ (paliperidone palmitate). The active ingredient of INVEGA SUSTENNA is paliperidone palmitate. The chemical name for paliperidone palmitate is [(9RS)-3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-9-yl] hexadecanoate, also known as C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Paliperidone palmitate has the following structural formula:



B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved NDA No.22-264 for INVEGA SUSTENNA for commercial marketing or use under §505 of the FDC Act on July 31, 2009. **Exhibit 2** and **Exhibit 3**

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

INVEGA SUSTENNA is a human drug product, the sole active ingredient of which is paliperidone palmitate. Neither paliperidone palmitate, nor any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

INVEGA™ (paliperidone) Extended Release Tablets is a human drug product, the sole active ingredient of which is paliperidone. INVEGA was approved by the FDA on December 19, 2006. Paliperidone is not a salt or ester of paliperidone palmitate.

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5))

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last date this application may be submitted is September 29, 2009.

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors:	Cornelus G.M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, and Jan Vandenberk
Patent No.	5,254,556
Date of Issue:	October 19, 1993
Date of Original Expiration:	October 27, 2009

A copy of the patent, including the entire specification (with claims) and drawings is attached as **Exhibit 4**.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statement is attached as **Exhibit 5.**

A terminal disclaimer pursuant to 37 C.F.R. §1.321(a) was filed in the '556 Patent disclaiming the terminal part of the statutory term of any patent which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§154-156 and 173 of U.S. Patent No. 5,158,952. A copy of the disclaimer is attached as **Exhibit 6**. The '556 Patent is commonly owned with U.S. Patent No. 5,158,952.

No certificate of correction or reexamination certificate has issued in the '556 Patent.

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '556 Patent claims the active ingredient of the Product approved which is paliperidone palmitate. The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

A claim chart that lists each applicable claim of the '556 Patent and demonstrates the manner in which each claim reads on the Product is attached as **Exhibit 7.**

K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Hal Brent Woodrow, the person signing below, acknowledge the applicants' duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein.

L. FEE (1.740(a)(14))

The Application fee due is $1,120.00 (37 C.F.R. § 1.740(a)(15) and § 1.20(j).

Authorization is hereby made to charge the amount of $1,120.00 to Deposit Account No. 10-0750/JAB0828/HBW.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 10-0750/JAB0828/HBW.

M. CORRESPONDENCE

Please direct all inquiries and correspondence relating to this application to:

Philip S. Johnson, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08816

Attn: Hal Brent Woodrow

Phone: (732) 524-2976
Facsimile: (732) 524-2808

N. COPIES (§ MPEP 2753 (8th Edition, Rev. No. 4))

Four additional copies of this application are attached, making a total of five copies being submitted.

Conclusion

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 5,254,556 is entitled to the requested 1449 day extension of its term to October 15, 2013.

Prompt action on this application is respectfully requested.

Date: 5 August 2009

Hal Brent Woodrow

Signature of Practitioner
Hal Brent Woodrow, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08816
U.S.A.

Reg. No.: 32,501
Tel. No.: 732-524-2976
Customer No.: 000027777

Exhibit 9

STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556

Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G.M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, and Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

Statement of Eligibility for Extension of Patent Term Due to Regulatory Review

I, Hal Brent Woodrow, represent that I am the attorney of record duly appointed by the assignee of the entire right, title and interest in the patent application identified above, and do state on behalf of the Applicant as follows:

To the best of my knowledge, U.S. Patent No. 5,254,556 (the '556 Patent) meets all of the eligibility criteria set forth in 37 C.F.R §§1.710 and 1.720 for extension of patent term.

The '556 Patent claims a "product" as that term is defined in 37 C.F.R §1.710, specifically the composition and use of a new human drug, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension 37 C.F.R §1.720(a).

The term of the '556 Patent has never been previously extended. 37 C.F.R §1.720(b).

An application for extension of the term of the '556 Patent in compliance with 37 C.F.R §1.740 is herewith submitted. 37 C.F.R §1.720(c).

The approved product, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, has been subject to a regulatory review period before its commercial marketing or use as defined in 35 U.S.C. §156(g). 37 C.F.R §1.720(d).

The approved product, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, has received permission for commercial marketing or use and the permission for the commercial marketing or use of the product is the first received permission for commercial marketing or use under the provision of law under which the applicable regulatory review occurred. 37 C.F.R §1.720(e).

The application for extension of the term of the '556 Patent submitted herewith is submitted within the sixty-day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred. 37 C.F.R §1.720(f).

The term of the '556 Patent, including any interim extension issued pursuant to § 1.790, has not expired before the submission of an application in compliance with 37 C.F.R. § 1.741. 37 C.F.R §1.720(g).

No other patent term has been extended for the same regulatory review period for the approved product, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, 37 C.F.R §1.720(h).

The extension claimed is 1449 days, setting the patent to expire on October 15, 2013. The following are the calculations, made in accordance with 37 C.F.R. § 1.775, that result in the claimed extension:

(1) The testing phase began on June 2, 2003 (the effective date of the IND) and ended on October 26, 2007 (submission date of the NDA).

(2) The approval phase began on October 26, 2007 (day of receipt by the FDA of the NDA) and approval was granted on July 31, 2009.

(3) The total number of days in the testing phase (from and including June 2, 2003 to and including October 26, 2007) is 1608 days from the start date to the end date, end date included. One half of the testing phase is 804 days.

(4) The total number of days in the approval phase is (from and including October 26, 2007 to and including July 31, 2009) is 645 days from the start date to the end date, end date included.

(5) The patent issued on October 19, 1993 before the regulatory approval process began.

(6) Applicant acted with due diligence throughout the entire regulatory review period.

(7) The sum of the (a) number of days in one half of the testing phase (804), and (b) number of days in the approval phase (645) is: 1449.

(8) The original expiration date of the patent is October 27, 2009.

(9) Addition of the extension of 1449 days to the original expiration date of the patent extends the expiration date of the patent to October 15, 2013.

(10) Fourteen years from the approval date of the product (July 31, 2009) is July 31, 2023.

(11) Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed 14 years from the date of product approval. The fourteen year cap does not apply since the extension of 1449 days sets the patent to expire on October 15, 2013, which is before the date that is 14 years post-approval (July 31, 2023).

(12) Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since the extension of 1449 days patent is less than five years.

(13) In light of the conclusions set forth above, the extended expiration date of the '556 Patent is believed to be October 15, 2013.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment,

or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 5 August 2009

Hal Brent Woodrow, Reg. No. 32,501

Hal Brent Woodrow, Esq.
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Reg. No.: 32,501
Tel. No.: 732-524-1495
Customer No.: 000027777

UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Ortho-McNeil-Janssen Pharmaceuticals, Inc.	:	
Request for Patent Term Extension	:	ORDER GRANTING
U.S. Patent No. 5,254,556	:	INTERIM EXTENSION

Ortho-McNeil-Janssen Pharmaceuticals, Inc., the owner of record in the United States Patent and Trademark Office (USPTO) of U.S. Patent No. 5,254,556, filed an application for patent term extension under 35 U.S.C. § 156 on August 6, 2009. The original term of the patent is due to expire on October 27, 2009. The patent claims paliperidone palmitate, labeled as the active ingredient in the human drug product Invega Sustenna™, which was approved by the Food and Drug Administration for commercial marketing or use on July 31, 2009. An extension of 1,449 days is requested.

The initial USPTO review of the application to date indicates that the subject patent is eligible for extension under 35 U.S.C. § 156. Because the original term of the patent would expire before a certificate of patent term extension can be issued or denied, an interim extension of the patent term is appropriate.

An interim extension under 35 U.S.C. § 156(e)(2) of the term of U.S. Patent No. 5,254,556 is granted for a period of one year from the original expiration date of the patent, i.e., until October 27, 2010.

10/7/09
Date

David J. Kappos
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Practitioner's Docket No. JAB0828USDIV ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993

Inventors: Cornelus G. M. Janssen Expiration Date: October 27, 2010

Title: 3-piperidinyl-1,2-benzisoxazoles

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR INTERIM EXTENSION OF PATENT TERM (37 C.F.R. § 1.760)

Dear Sir:

Applicant hereby requests an Interim Patent Term Extension for a period of one (1) year as is provided under 35 U.S.C 156(e)(2) and 37 CFR 1.760 from October 27, 2010 until October 27, 2011 to allow for additional time for reviewing and granting applicants' previously filed Application for Patent Term Extension.

BACKGROUND

An initial application for Interim Extension of Patent Term pursuant to 37 CFR 1.790 was file on July 7, 2009 for US Patent 5,254,556 ('556 Patent). The '556 Patent claims the active ingredient of the INVEGA SUSTENNA™ Extended-Release Injectable Suspension which has undergone regulatory review which is paliperidone palmitate. The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

The FDA on July 31, 2009 granted a marketing authorization for the INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension which was under regulatory review under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

An Application for Patent Term Extension in compliance with 37 CFR 1.740 and an Application for Interim Extension of Patent Term under 37 CFR 1.760 were filed August 6, 2009.

The first request for Interim Patent Extension of the Patent Term was granted on or about October 7, 2009 by the very honorable Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, David J. Kappos.

The above-identified patent expires on October 27, 2010, more than three months for the date of this application.

FEE STATUS

Authorization is hereby made to charge the amount of $220.00 to Deposit Account No. 10-0750/JAB0828/HBW.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

Four additional copies of this application are attached, making a total of five copies being submitted (See§ MPEP 2753 (8th Edition).

Date: 20 July 2010

Hal Brent Woodrow

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732-524-2976
Customer No. 27777

UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Ortho-McNeil-Janssen Pharmaceuticals, Inc.	:	
Request for Patent Term Extension	:	ORDER GRANTING
U.S. Patent No. 5,254,556	:	INTERIM EXTENSION

Ortho-McNeil-Janssen Pharmaceuticals, Inc., the owner of record in the United States Patent and Trademark Office (USPTO) of U.S. Patent No. 5,254,556, filed an application for patent term extension under 35 U.S.C. § 156 on August 6, 2009. The original term of the patent expired on October 27, 2009. The patent claims paliperidone palmitate, labeled as the active ingredient in the human drug product Invega Sustenna®, which was approved by the Food and Drug Administration for commercial marketing or use on July 31, 2009. An extension of 1,449 days is requested.

The initial USPTO review of the application to date indicates that the subject patent is eligible for extension under 35 U.S.C. § 156. Because the extended term of the patent would expire before a certificate of patent term extension can be issued, an additional interim extension of the patent term is appropriate.

A second interim extension under 35 U.S.C. § 156(e)(2) of the term of U.S. Patent No. 5,254,556 is granted for a period of one year from the extended expiration date of the patent, i.e., until October 27, 2011.

October 1, 2010

Date

David J. Kappos

David J. Kappos
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Practitioner's Docket No. JAB0828USDIV ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993

Inventors: Cornelus G. M. Janssen Expiration Date: October 27, 2011

Title: 3-piperidinyl-1,2-benzisoxazoles

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR INTERIM EXTENSION OF PATENT TERM (37 C.F.R. § 1.760)

Dear Sir:

Applicant hereby requests a third Interim Patent Term Extension for a period of one (1) year as is provided under 35 U.S.C 156(e)(2) and 37 CFR 1.760 from October 27, 2011 until October 27, 2012 to allow for additional time for reviewing and granting applicants' previously filed Application for Patent Term Extension.

BACKGROUND

An initial application for Interim Extension of Patent Term pursuant to 37 CFR 1.790 was filed on July 7, 2009 for US Patent 5,254,556 ('556 Patent). The '556 Patent claims the active ingredient of the INVEGA SUSTENNA™ Extended-Release Injectable Suspension which has undergone regulatory review which is paliperidone palmitate. The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

The FDA on July 31, 2009 granted a marketing authorization for the INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension which was under regulatory review under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

An Application for Patent Term Extension in compliance with 37 CFR 1.740 and an Application for Interim Extension of Patent Term under 37 CFR 1.760 were filed August 6, 2009.

The first request for Interim Patent Extension of the Patent Term was granted on or about October 7, 2009 by the very honorable Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, David J. Kappos. The first Interim Patent Extension extended the term of the '556 patent from October 27, 2009 until October 27, 2010.

The second request for Interim Patent Extension of the Patent Term was granted on or about October 1, 2010 by the very honorable Under Secretary of Commerce for Intellectual Property and Director of the

United States Patent and Trademark Office, David J. Kappos. The second Interim Patent Extension extended the term of the '556 patent from October 27, 2010 until October 27, 2011.

The above-identified patent expires on October 27, 2011, more than three months from the date of this application.

FEE STATUS

Authorization is hereby made to charge the amount of $220.00 to Deposit Account No. 10-0750/JAB0828/HBW.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

Four additional copies of this application are attached, making a total of five copies being submitted (See§ MPEP 2753 (8th Edition).

Date: June 10, 2011

/Hal Brent Woodrow/

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UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Ortho-McNeil-Janssen Pharmaceuticals, Inc.	:	
Request for Patent Term Extension	:	ORDER GRANTING
U.S. Patent No. 5,254,556	:	INTERIM EXTENSION

Ortho-McNeil-Janssen Pharmaceuticals, Inc., the owner of record in the United States Patent and Trademark Office (USPTO) of U.S. Patent No. 5,254,556, filed an application for patent term extension under 35 U.S.C. § 156 on August 6, 2009. A second request for interim extension was filed on June 13, 2011. The extended term of the patent expires on October 27, 2011. The patent claims paliperidone palmitate, the active ingredient in the human drug product Invega Sustenna®, which was approved by the Food and Drug Administration for commercial marketing or use on July 31, 2009. An extension of 1,449 days is requested.

The USPTO review to date of the application to date indicates that the subject patent is eligible for extension of the patent term under 35 U.S.C. § 156. A final determination of the length of the extension of the patent term and issuance of a patent term extension certificate cannot be made until a final determination of the length of the regulatory review period is made. Because the extended term of the patent would expire before a certificate of patent term extension can be issued, a second interim extension of the patent term is appropriate.

A second interim extension under 35 U.S.C. § 156(e)(2) of the term of U.S. Patent No. 5,254,556 is granted for a period of one year from the extended expiration date of the patent, i.e., until October 27, 2012.

September 30, 2011

Date

David J. Kappos

David J. Kappos
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Practitioner's Docket No. JAB0828USDIV ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556

Issued: October 19, 1993
Expiration Date: October 27, 2012

Inventors: Cornelus G. M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, Jan Vandenberk

Title: 3-piperidinyl-1,2-benzisoxazoles

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR INTERIM EXTENSION OF PATENT TERM (37 C.F.R. § 1.760)

Dear Sir:

Applicant hereby requests a fourth Interim Patent Term Extension for a period of eleven months and approximately 19 days as is provided under 35 U.S.C 156(e)(2) and 37 CFR 1.760 from October 27, 2012 until the expiration of the extended patent term on or about October 15, 2013 to allow for additional time for reviewing and granting applicants' previously filed Application for Patent Term Extension.

BACKGROUND

An initial application for Interim Extension of Patent Term pursuant to 37 CFR 1.790 was filed on July 7, 2009 for US Patent 5,254,556 ('556 Patent). The '556 Patent claims the active ingredient of the INVEGA SUSTENNA™ Extended-Release Injectable Suspension, paliperidone palmitate, which has undergone regulatory review. The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

The FDA on July 31, 2009 granted a marketing authorization for the INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, which was under regulatory review under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

An Application for Patent Term Extension in compliance with 37 CFR 1.740 and an Application for Interim Extension of Patent Term under 37 CFR 1.760 were filed August 6, 2009.

The first request for Interim Patent Extension of the Patent Term was granted on or about October 7, 2009 by the very honorable Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, David J. Kappos. The first Interim Patent Extension extended the term of the '556 patent from October 27, 2009 until October 27, 2010.

The second request for Interim Patent Extension of the Patent Term was granted on or about October 1, 2010 by the very honorable Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, David J. Kappos. The second Interim Patent Extension extended the term of the '556 patent from October 27, 2010 until October 27, 2011.

The third request for Interim Patent Extension of the Patent Term was granted on or about September 30, 2011 by the very honorable Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, David J. Kappos. The third Interim Patent Extension extended the term of the '556 patent from October 27, 2011 until October 27, 2012.

The above-identified patent expires on October 27, 2012, more than three months from the date of this application.

FEE STATUS

Authorization is hereby made to charge the amount of $220.00 to Deposit Account No. 10-0750/JAB0828/HBW.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

Four additional copies of this application are attached, making a total of five copies being submitted (See§ MPEP 2753 (8th Edition).

Date: July 24, 2012

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UNITED STATES PATENT AND TRADEMARK OFFICE

In re Ortho-McNeil-Janssen Pharmaceuticals, Inc.	:	
Request for Patent Term Extension	:	ORDER GRANTING
U.S. Patent No. 5,254,556	:	INTERIM EXTENSION

Ortho-McNeil-Janssen Pharmaceuticals, Inc., the owner of record in the United States Patent and Trademark Office (USPTO) of U.S. Patent No. 5,254,556, filed an application for patent term extension under 35 U.S.C. § 156 on August 6, 2009. A fourth request for interim extension was filed on July 25, 2012. The extended term of the patent expires on October 27, 2012. The patent claims paliperidone palmitate, the active ingredient in the human drug product Invega Sustenna®, which was approved by the Food and Drug Administration for commercial marketing or use on July 31, 2009. An extension of 1,449 days is requested.

The USPTO review of the application to date indicates that the subject patent is eligible for extension of the patent term under 35 U.S.C. § 156. A final determination of the length of the extension of the patent term and issuance of a patent term extension certificate has not been made. Because the extended term of the patent would expire before a certificate of patent term extension can be issued, a fourth interim extension of the patent term is appropriate.

A fourth interim extension under 35 U.S.C. § 156(e)(2) of the term of U.S. Patent No. 5,254,556 is granted until October 15, 2013.

September 27, 2012

Date

David J. Kappos

David J. Kappos
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office